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Frank A. **Maffei**
Robert F. **Tamburro**
Arno **Zaritsky**
Editors

PEDIATRIC CRITICAL CARE

TEXT AND STUDY GUIDE

Second Edition

Springer

Pediatric Critical Care

Steven E. Lucking • Frank A. Maffei
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Preface

The multidisciplinary nature of pediatric critical care medicine creates a considerable challenge to those who seek to master the discipline. The knowledge that the critical care pediatrician must possess encompasses aspects of many different organ-based specialties. Our goal for this text is to help young critical care physicians review and master fundamental principles of our specialty for the purpose of achieving certification. In addition, we hope that the text will be a practical resource for the practice of pediatric critical care incorporating concepts of pathophysiology, therapeutic theory, and management principals.

We are indebted to our authors for their willingness to share their considerable expertise and contribute to this labor. We are grateful for their efforts and their patience as we navigated the pitfalls in getting the work completed.

We hope that the text will help the practitioner achieve success in the practice of pediatric critical care medicine. The care of children is both a privilege and a blessing. To care for children at their most vulnerable time cannot help but provide the practitioner with awe for the beauty of life and the resilience of the child's spirit, a respect for the power of a parent's love, and an appreciation of the blessing of our own children's health.

Steven E. Lucking, MD
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Acknowledgments

When we first began this endeavor years ago, we were told by many experienced colleagues that putting together a quality textbook is a labor of love, a greater truth has not been told. However, when we were told a second edition would be so much easier than the first, that turned out to be not so true.

The work has been difficult at times, but always rewarding and worthwhile. As editors, we are proud of the textbook, but clearly recognize that the project would never have come to fruition without key individuals who have supported us through this arduous process.

To our wives: Lynn, Tricia, Janet, and Peggy, who supported and guided us throughout the entire project. Without their love, wisdom, and tireless support, this book would have never reached completion.

To our children, who serve as the inspiration and guiding force for each of us.

To the authors of every chapter. Without their intellect, hard work, and drive to teach, the dissemination of this important knowledge to the next generation of pediatric intensivists would not be possible. We particularly want to thank our authors for their efforts during the late stages of the publication when many of them assumed increased clinical and administrate duties in response to the COVID-19 pandemic. On that note, the editors decided not to include a separate section on the SARS CoV-2 virus and the pandemic as the data was still in evolution and publication of an evidence based chapter would have been premature.

Two additional special acknowledgements:

We want to thank and acknowledge our Co-editor, Dr. Steven Lucking. After 35 years of service as a Pediatric Intensivist, Steve will be turning his attention to travel, baseball, and serving as a pediatrician on medical missions. Steve has been a foundational and transformative leader in the field of pediatric critical care. He has been the quintessential bedside intensivist—shepherding our sickest children through the rigors of critical illness. He has served as a mentor to many—always placing the academic achievements of his colleagues above his own. Always an advocate, critical thinker, and most importantly a selfless friend.

Lastly, my wife Lynn Maffei, who during the writing of the second edition, developed a health crisis. She has been the model of courage, perseverance, and faithfulness. Our love can and will overcome all.

» God watches over small children and fools…he has us all covered.

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Essential Physiologic Principles

Contents

Genomics and Genetic Predisposition to Critical Illness in the Pediatric Intensive Care Unit

Mary K. Dahmer and Michael W. Quasney

Contents

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1

Learning Objectives

- Understand the basics of human genetics, including terminology related to inheritance, predisposition to human disease, and gene expression.
- Review advances that have been made in the field of human genomics and genetic research into the development of critical illness.
- Discuss genetic variants in genes that predispose certain individuals to critical illness or protect individuals from the development of certain critical illnesses.

1.1 Introduction

Advances continue to be made in the understanding of the contribution of genetics to the development of human disease, including illnesses found specifically in the intensive care unit (ICU). With the mapping of the human genome and ongoing mapping of genetic polymorphisms and haplotypes in humans, the field of critical care medicine has now begun to study the impact of genetics on common illnesses, such as sepsis and acute respiratory distress syndrome (ARDS), that affect children who require critical care. In addition, how differences of the host defense response lead to variable outcomes in outwardly appearing similar disease states and how genetic differences in response to therapy will help practitioners tailor therapeutic interventions to an individual child's genetic composition can be examined. While we are still years away from true individualized medicine, we are now closer than ever to understanding why two children might respond to the same environmental insult in vastly different ways.

Before being able to appreciate the advances in research that have been accomplished in relation to the genetic impact on critical illness in children, it is important to understand the basics of human genetics and become familiar with the terminology that is utilized to discuss these remarkable advances. Once the genetic basics are clear, genetic variants that may impact critical illness in children will be discussed.

1.2 Human Genetics

1.2.1 Structure and Function of Genes

The order of nucleotide bases is termed the sequence and is read in the 5′ to 3′ direction.

The nucleus of all cells holds chromosomes that contain deoxyribonucleic acid (DNA), the genetic material that is inherited from parents. DNA is responsible for determining the structure of the cell, the function and activity of the cell in response to various stimuli, and the interaction the cell has with other cells and the extracellular environment. The DNA molecule consists of two chains of deoxyribonucleotides held together by complementary base pairs. The deoxyribonucleotides contain the four nucleotide bases, adenine (A), thymine (T), guanine (G), and cytosine (C) that are covalently bound together by phosphodiesterase bonds linking the 5′ carbon of one deoxyribose group to the 3′ carbon of the next group. The two chains of deoxyribonucleotides are linked by hydrogen bonds between the A's of one strand and the T's of the other. Likewise, the G's of one strand are linked by hydrogen bonds to the C's of the complementary strand. These two complementary strands form the DNA double helix (Fig. 1.1), with one strand running in the 5′ to 3′ direction while the other strand runs in the 3′ to 5′ direction. The order of nucleotide bases is termed the *sequence* and is read in the 5′ to 3′ direction. The genetic

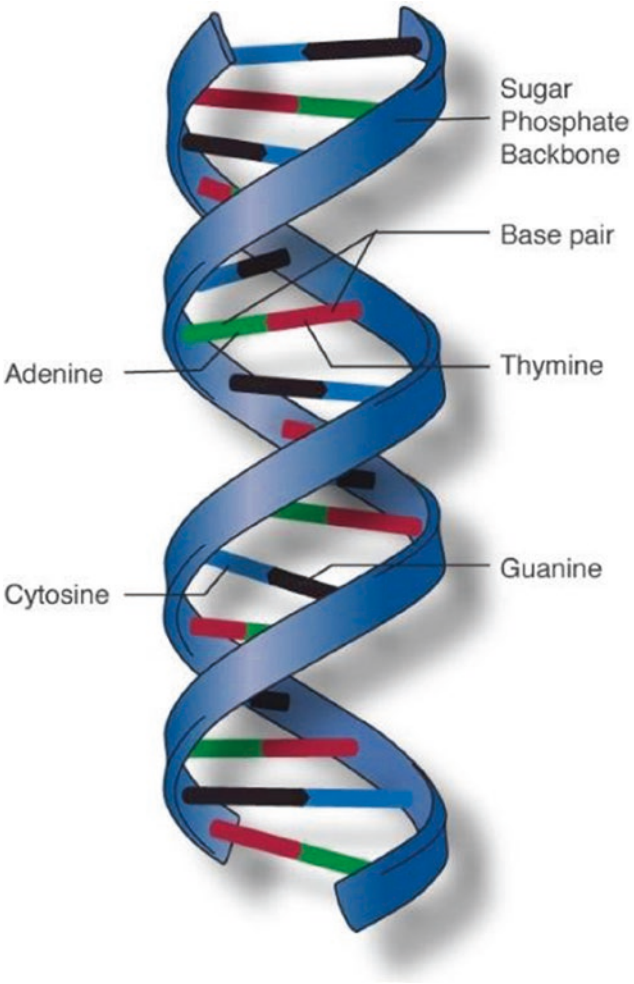

Fig. 1.1 The four nucleotides of the DNA double helix. (Courtesy: National Human Genome Research Institute ► http://www.genome.gov/glossary.cfm#s)

information of an individual is encoded by the precise positioning and order of these base pairs.

The entire DNA content of an organism is their genome.

The entire DNA content of an organism is their *genome*. Every cell of an organism contains two copies of the DNA, with the exception of red blood cells, which lack a nucleus and DNA, and sperm and egg cells, which contain one copy of the DNA. Humans have 46 chromosomes, including 22 pairs of autosomal chromosomes and one pair of sex chromosomes. Each chromosome is made up of a centromere and two telomeres (ends) (Fig. 1.2). The two arms of the chromosome are the short arm (p) and long arm (q). The parts of the genome that contain nucleotide sequences that code for the basic physical and functional units of heredity are the *genes*. It is estimated that the human genome contains about 20,000–25,000 genes. Most genes code for proteins, although some genes code for ribonucleic acid (RNA) involved in assembling proteins (transfer RNA and ribosomal RNA) or RNAs, which regulate gene activity. The structure of genes is very complex and highly variable. Genes which code for proteins are made up of a variable number of *exons*, which contain the actual coding sequence for the proteins, and *introns*, which are noncoding regions which separate the exons (Fig. 1.3). While the function of the introns is unclear, some disease processes have been found to be associated with certain nucleotide variations located in these intron regions. Genes also have regulatory regions, including promoter sequences that generally reside at the 5′ end of the gene (referred to as upstream) and regions at the

Genes are made up of a variable number of exons, which contain the actual coding sequence for the proteins, and introns, which are noncoding regions which separate the exons.

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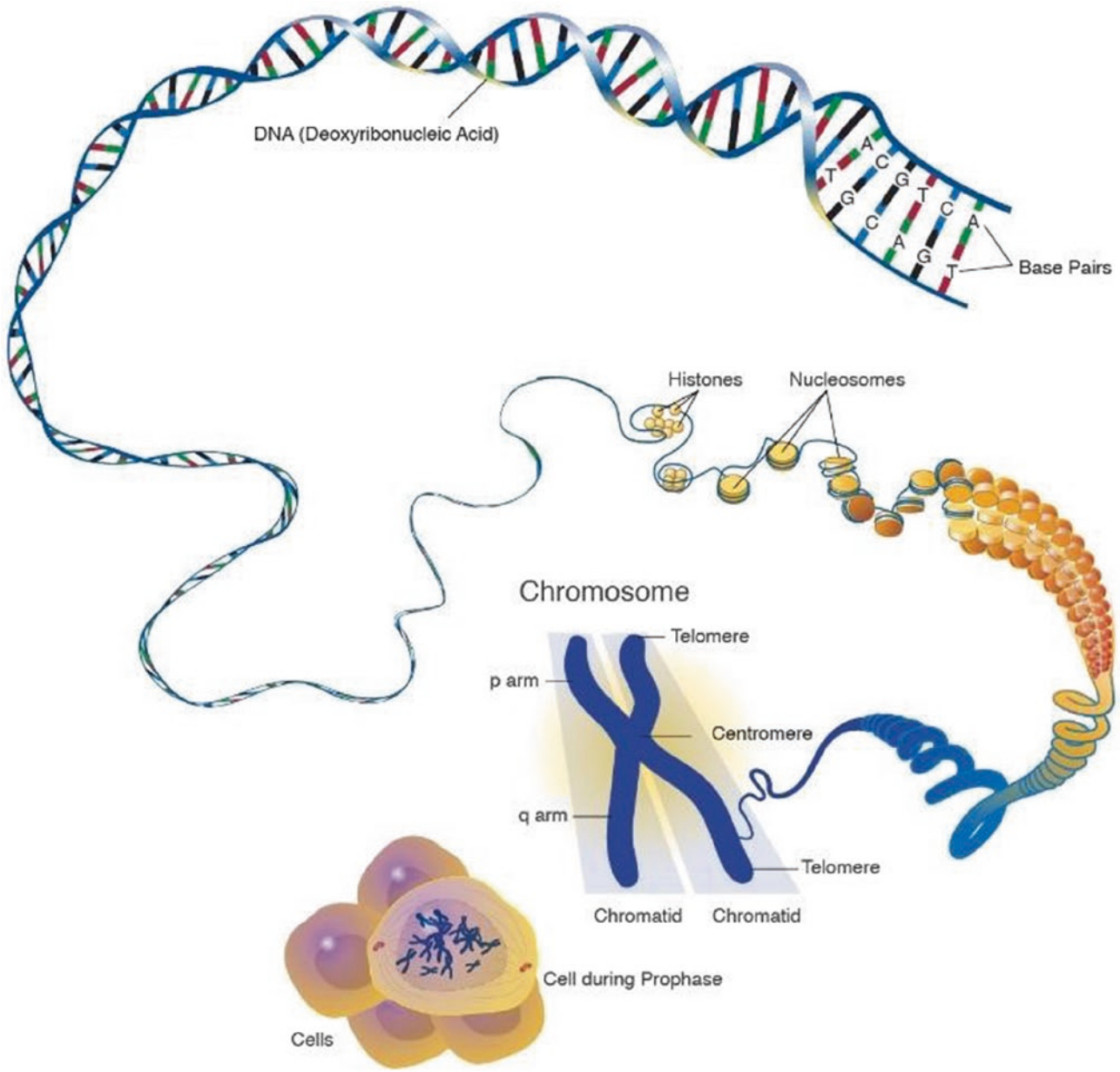

Fig. 1.2 The structure of a chromosome. (Courtesy: National Human Genome Research Institute ► http://www.genome.gov/glossary.cfm#s)

3′ end associated with the stability of the mRNA. In some cases, regions within introns act as regulatory regions.

Another important concept in genetics is the *locus*, which refers to a specific site or position on a chromosome and can refer to either a gene or a specific genetic variant (variation in the DNA sequence). The sequencing of the human genome revealed that the genome contains many sites, where the base pair present at a locus differs between individuals. It is important to remember that as individuals contain two copies of each chromosome (with the exception of chromosomes X and Y), a locus will have two copies of the gene or nucleotide of interest, one coming from each chromosome. Consequently, an individual may have two slightly different sequences for a specific gene because the nucleotides within that gene have sites that differ between the two copies. These

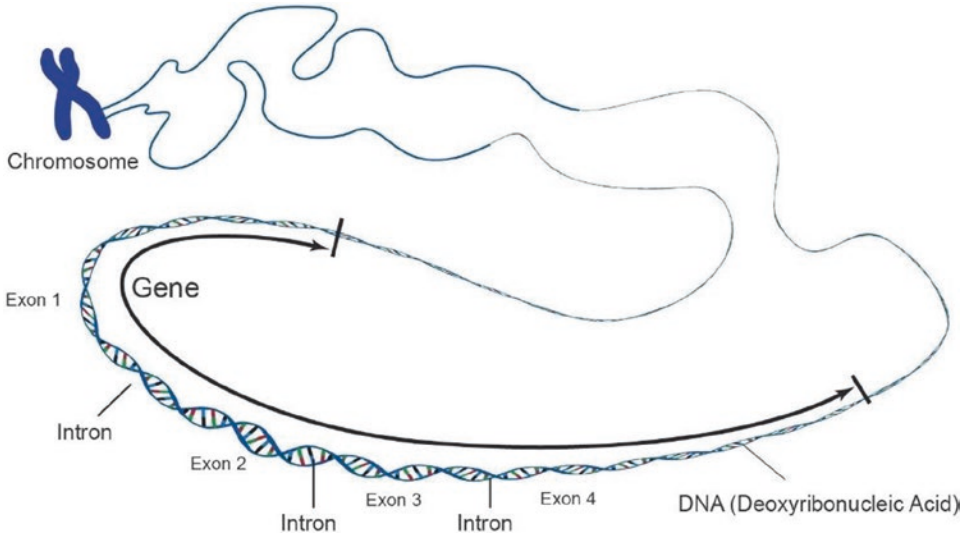

Fig. 1.3 The structure of a gene, including the exons (coding sequence) and introns (noncoding sequence). (Courtesy: National Human Genome Research Institute ► http://www.genome.gov/glossary.cfm#s)

alternative forms of a gene are termed *alleles*, or *variants*. The term allele or variant can refer to either a gene or a specific nucleotide position (locus), where there is a genetic variant within the gene. The alleles present in a specific individual at a genetic locus is that person's *genotype*. The genotype may refer to the whole gene, or more commonly to a specific nucleotide within a gene. An example is the surfactant protein B (SP-B) +1580 site. An individual's genotype at that site may either be TT, CT, or CC. Individuals are *heterozygous*, if they possess two different alleles at the locus of interest, and *homozygous*, if they possess two identical alleles at that locus.

1.2.2 Genetic Recombination and Mapping of Genes and Genetic Variants

There are many potential benefits of identifying genes/gene variants involved in disease. These include, but are not limited to, an improved understanding of the disease etiology, insight into the mechanisms of disease pathogenesis, an ability to develop an early disease risk assessment, the potential to discover novel therapeutic drug targets, the ability to estimate the therapeutic response to specific pharmacologic therapies, the possibility of targeted disease prevention strategies to be utilized in high-risk populations based on genetic predisposition, and the movement from the classic symptoms-based disease definition toward a true molecular definition of complex disease processes.

Before the sequencing of the human genome, *linkage analysis*, which is related to genetic recombination, was the predominant method of identifying and mapping disease causing genes in the genome. *Genetic recombination* is the reshuffling of genes from generation to generation and is the basis of genetic diversity in sexually reproducing organisms. Genetic recombination results in an exchange of genetic material between homologous chromosome pairs, which results in segments of DNA being exchanged with the other chromosome of the pair, thereby shuffling the genetic material. Linkage analysis relies on the genetic recombination frequency between two loci on a single chromosome to identify locations in the chromosome associated with disease. Recombination frequencies can be measured by genotyping individuals for the loci of interest in a family pedigree. The closer together two loci are on a chromosome, the lower the likelihood of recombination occurring between them.

If loci are very close, they are said to be linked. In linkage analysis, the reliability of genetic linkage between loci is determined using the *LOD score*, which is an estimate of whether two loci are likely to lie near each other on a chromosome and are therefore likely to be inherited together. A LOD score of 3 or more, which represents odds of 1000:1 or greater in favor of linkage, is used to indicate statistically significant linkage and, therefore, concludes that the two loci of interest are close. This approach has been used to identify and map genes responsible for disease to a particular location in the genome based on being inherited with respect to a locus of known map location, with the assumption of no genetic recombination.

Linkage disequilibrium (LD), often referred to as allelic association, is a measure of physical association between two alleles and occurs when closely linked alleles are inherited together during many generations.

With the completion of the Human Genome Project in 2003, which sequenced the human genome, there was no need to use linkage analysis to determine the location of a variant within the genome. However, it became clear that even after recombination over generations, many variants are inherited together, and these variants are said to be in *linkage disequilibrium* (LD). LD refers to the nonrandom association of alleles (or variants). LD is a measure of physical association between two alleles and occurs when closely linked alleles are inherited together during many generations. Therefore, if variants are in LD, the presence of one variant can be used to study the other.

A haplotype represents a combination of polymorphic alleles on a single chromosome delineating a pattern that is inherited together and transmitted from parent to offspring.

A *haplotype* represents a combination of two or more variants on a single chromosome delineating a pattern that is inherited together and transmitted from parent to offspring. Haplotype analysis is a useful tool for analysis of disease gene discovery, as investigators may capitalize on the fact that many of the variants of interest are not transmitted independently of each other, and the presence of one gene variant can tag the presence of another variant from the same chromosome. In some cases, haplotype assessment can provide a higher level of specificity, sensitivity, and accuracy in "true" associations with disease risk or severity. By focusing on haplotypes as well as single-nucleotide variants, researchers are now able to more accurately study genetic predisposition to various diseases of interest. With the recent report of the International HapMap Consortium and the identification and cataloging of haplotypes now available, the utility of this type of study is brought into focus as an important tool to guide genetic association studies on complex human diseases. However, the degree of LD between variants and the type and frequency of haplotypes differs significantly between races and ethnicities. Consequently, race and ethnicity need to be considered and accounted for in genetic association studies.

1.2.3 Genetic Mutations and Other Genetic Variants

Genetic mutations are rare changes that occur in the sequence of DNA that occur in less than 1% of the population.

Genetic mutations are changes that occur in the sequence of DNA. The term mutation generally refers to rare changes (present in less than 1% of the population) that are detrimental or that cause disease. Mutations can be classified as somatic mutations, which occur in somatic cells and are not commonly passed onto offspring, and germline mutations, which occur in the reproductive cells and are passed onto offspring. There are several different types of mutations. *Translocations* are large-scale mutations consisting of switching of chromosomal regions between one chromosome and another chromosome. Mutations can also consist of single changes in the nucleotide bases and include substitution, deletion, or insertion of nucleotides. Insertions and deletions can also involve hundreds of nucleotides. Mutations that occur in the coding regions can have several consequences: they can change the amino acid of the protein at a single site; they can cause a premature stop codon resulting

in early termination of translation, and, consequently, lead to a truncated protein; or they may have no effect at all if the mutation leads to a nucleotide substitution that does not alter the amino acid. Likewise, mutations in noncoding regulatory regions (such as promoters) may also affect the expression of the gene by altering the quantity of mRNA transcribed and, hence, the level of the protein. Mutations in the intron/exon boundary region may also lead to incorrectly spliced mRNAs and result in significantly different proteins or differences in levels of protein products.

The mutations discussed in the preceding paragraph are variations which are rare. However, it is estimated that the human genome contains over 10 million relatively common genetic variants that occur at a frequency greater than 1% in the population which are referred to as *polymorphisms*. If the polymorphism is a change in a single nucleotide, it is referred to as a *single-nucleotide polymorphisms (SNPs)*. It is now clear that most genes are polymorphic, that is, they contain multiple sites that vary between individuals. *Copy number variants (CNVs)* are stretches of DNA of greater than 1 kb that show differences in the expected number of copies of the DNA in greater than 1% of the human population. Very recently, it has become clear that CNVs are also common in human genomes and contribute significantly to human genetic variation. The differences in the nucleotide sequence described above are what give rise to our genetic variability; they account for inherited differences in our physical traits and the way we respond to environmental stimuli and medications. While the majority of these nucleotide variations do not cause a disease, some genetic variations may influence the development of certain diseases. These more common genetic variations, whether SNPs or small insertions or deletions of nucleotides, are the ones currently being examined in many studies for associations with susceptibility to and outcome from diseases seen in the intensive care unit setting.

Polymorphisms are variations that occur at a frequency greater than 1% in the population; if the polymorphism is a change in a single nucleotide, it is referred to as a single-nucleotide polymorphism (SNP).

Genetic polymorphisms, like the rarer mutations, may influence the functional activity of the protein product or may influence the quantity of the mRNA made if present in a regulatory region. There has been an explosion of studies attempting to determine if these genetic polymorphisms may account for some of the clinical variability we as clinicians observe at the bedside in the ICU. For example, can the difference in disease severity between two children with pneumonia be associated with variations in their genes coding for one of the surfactant proteins?

1.2.4 Gene Expression

Gene expression is the process by which the information contained within genes is used to make proteins (Fig. 1.4). This occurs by a combination of two distinct processes: transcription and translation. *Transcription* is the process by which the genetic information in DNA is transcribed into messenger RNA (mRNA). mRNA differs from DNA in that it is single-stranded, has a modified sugar backbone, and contains uracil (U) instead of T. The process of transcription involves the unwinding of the two complementary strands of DNA, the enzyme RNA polymerase binding to the promoter region of a gene on a single strand of DNA, and synthesizing the mRNA molecule by adding ribonucleotides in an order that is complementary to the DNA strand. The transcribed mRNA thus contains all the genetic information between the transcriptional start and stop sites on the DNA, including exons and introns. The noncoding intron sequences are removed by a process referred to as splicing, which connects all the exons together to form the final mRNA product. This mRNA represents the coding DNA sequences for a single gene. (It should be

Gene expression is the process by which the information contained within genes is used to make proteins.

Transcription is the process by which the genetic information in DNA is transcribed into messenger ribonucleic acid (mRNA).

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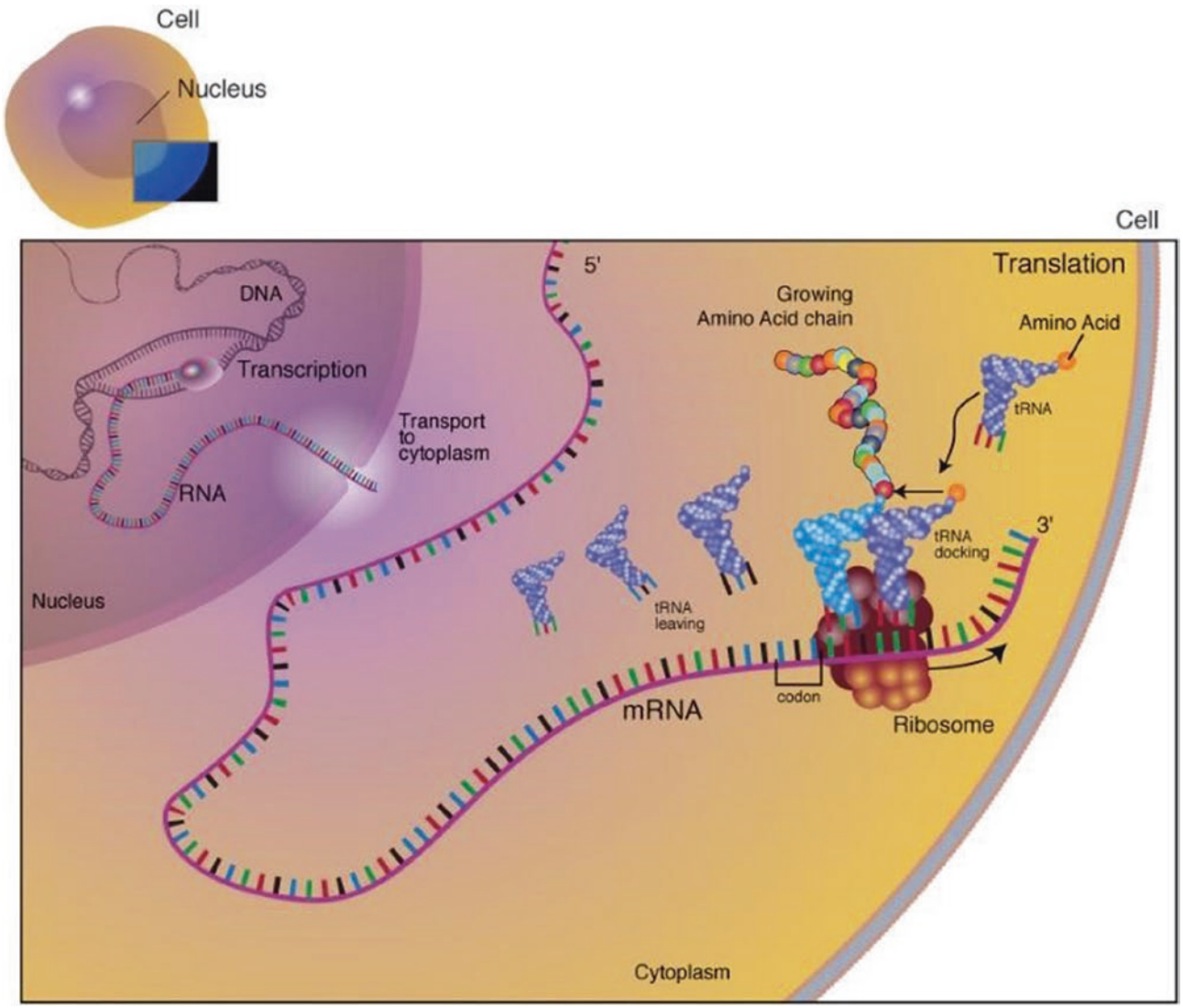

Fig. 1.4 Gene expression (transcription and translation), the process by which proteins are synthesized based on the information coded on DNA. (Courtesy: National Human Genome Research Institute ► http://www.genome.gov/glossary.cfm#s)

Translation is the process by which the genetic information from mRNA is utilized to guide the synthesis of proteins.

noted that splicing variations have been identified that influence disease processes that impact the final protein product by altering the mRNA sequences that are spliced together.) The mRNA is then transported to the cytoplasm and *translation* occurs, in which the genetic information from mRNA is utilized to guide the synthesis of proteins. Proteins are composed of amino acids. There are 20 different amino acids in humans, and each is encoded by a set of 3 nucleotides in the mRNA. These three nucleotides are called triplets or *codons*. The corresponding *anticodon* on the transfer RNA (tRNA) links with a codon, presenting its unique amino acid in the process of translational protein synthesis.

Since all cells that contain a nucleus carry the full set of genetic information, it is necessary for gene expression to be selective and tightly controlled, in a way that guarantees specific proteins are expressed in specific cells under appropriate conditions. This differential expression of genes ensures that cells develop correctly, can differentiate and function as specialized cells, and can mount various responses to external stimuli. In certain disease states, expression of specific genes may change, thereby providing a clue as to which genes

may be important in that disease process. Recent advances in technology have provided a valuable tool to evaluate the expression of genes during various diseases, including sepsis. These technologies include gene expression microarrays and RNA sequencing. Genome-wide expression microarrays contain small strands of DNA (which act as probes), representing all the genes in the genome attached to a solid substrate, such as a glass slide or silicon chip. mRNA is isolated from, for example, blood from patients with sepsis and controls without sepsis. If mRNA from a specific gene is present, it will hybridize to its complementary sequence on the microarray, and its signal is related to the amount of mRNA present. The comparison of array results between those with and without sepsis will indicate which genes' expression is altered in sepsis. In this fashion, one can identify specific genes that are expressed in the development of sepsis. Several examples of the use of this technology in the critically ill patient have been published, which have aided our understanding of the pathophysiology of certain ICU-specific diseases.

1.2.5 Phenotype

The observable characteristics of an individual define that individual's phenotype.

Up to this point, we have discussed the structure of DNA and the process of getting from the code in the DNA to protein. It is the functional aspects of these proteins that give rise to the observed traits, whether it be the color of one's eyes, the rate of metabolism of a drug, or the efficiency with which a protein receptor on a cell surface recognizes a pathogen. The observable characteristics of an individual define that individual's *phenotype*. This may include common physical and biochemical characteristics but can also describe a person's disease status (such as in cystic fibrosis). Phenotypes caused by mutations in a single gene may show *Mendelian inheritance patterns*. These patterns can be autosomal dominant (where a single copy of the gene causes the phenotype), autosomal recessive (where both copies of the gene are necessary for the phenotype), or sex linked (where the mutation occurs on the X chromosome). It is crucial to note that Mendelian inheritance patterns are seen only for single-gene disorders. Critical care diseases and syndromes, such as sepsis and ARDS, are complex disorders, whose genetic predisposition to the development of the disease is much more complex and likely involves multiple genes and other factors, such as environmental exposures. The multifaceted gene-gene and gene-environment interactions make the study of these diseases extremely complex.

1.3 Genetics of Common Complex Disorders

Disease aggregation may be due to complex genetic factors, the interaction of multiple genes on the development of the disease of interest, a host of environmental factors which place the individual at risk for the disease, or, most commonly, a combination of all of the above factors.

There are many common complex disorders that display obvious familial aggregation of cases but have no clear Mendelian inheritance patterns. The most commonly studied in medicine are cancer, diabetes, hypertension, and obesity, among others. The disease aggregation may be due to complex genetic factors, the interaction of multiple genes on the development of the disease of interest, a host of environmental factors which place the individual at risk for the disease, or, most commonly, a combination of all of the above factors (◘ Fig. 1.5). In other words, a person's genetic background may make them prone to a specific disease; a person may have *susceptibility gene variants* or susceptibility genes. Due to their inherited genetic makeup, the individual is at a higher inborn risk for developing the disease of interest but only if they are exposed to the environmental stressor that is known to associate with the disease. The susceptibility gene variant will not lead directly to the disease but

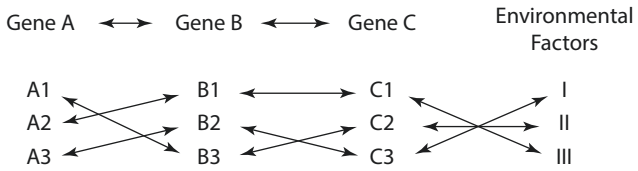

Fig. 1.5 The complex interactions that can occur between genes that may impact a disease process (gene-gene interaction) as well as between the genes of interest and environmental factors (gene-environment interaction)

will put that person at a higher risk if they are exposed to the environmental risk. For example, individuals may possess a susceptibility gene variant for the development of lung cancer, but this will lead to the development of cancer only if they are subject to a known environmental risk factor, such as smoking. Alternatively, a newborn may possess one or more susceptibility gene variants for the development of bronchopulmonary dysplasia, but if they are not born prematurely and do not require mechanical ventilation in the newborn period (and therefore are not subject to the environmental stressors known to impact the development of this lung disease), they will never develop this disease despite being genetically susceptible.

Gene variants can also decrease the susceptibility, or increase the resistance against a disease. These are *protective gene variants*. To give an example, there are individuals who smoke their entire adult lives and yet never develop chronic obstructive pulmonary disease. It is likely that these individuals possess protective gene variants against the development of this disease, even in the face of a strong environmental insult. A person may possess both susceptibility and protective genetic variants for the same disease, and the mix of these variants will together impact the overall genetic risk of that person to the disease of interest. This resultant genetic risk interacts also with the environmental risk of the individual, leading to the overall risk of that person developing the disease. In critical care, it is unlikely that one gene will cause the diseases that are treated in the ICU; it is more likely that multiple genes will interact with multiple environmental insults to predispose individuals to disease processes resulting in an overall risk for an individual patient to develop a certain disease of interest. Interestingly, certain populations seem to be immune to certain complex diseases. Examples include the Australian aborigines and Inuits from Greenland, in which both populations appear to be resistant to the development of type 1 diabetes. It is plausible that the disease resistance observed in these populations is due to absence of susceptibility gene variants or presence of protective gene variants in the group's gene pool.

Critical care diseases and syndromes, such as sepsis and ARDS, are complex disorders where genetic predisposition to the development of the disease is much more complex and likely involves multiple genes and other factors, such as environmental exposures. There are two hypotheses addressing the involvement of genetic variants in non-Mendelian inherited diseases or predispositions. One hypothesis is that the genetic component of these diseases or predispositions is due to the combination of many common (15–50) genetic variants acting together. Genome-wide association studies which genotype individuals at 1–2 million variant sites across the genome are used to identify common variants associated with disease. Thus far, many studies examining the impact of common genetic variants on disease have explained only a small component of the heritability of such disease. Consequently, a new hypothesis proposes that these multifactorial diseases and predispositions are due to the combination of a smaller number of more rare polymorphisms. Such rare variants will likely need to be identified by either exome sequencing (sequencing

only the DNA contained in exons coding for proteins) or whole genome sequencing. Exome and whole genome sequencing are expensive and consequently have not been widely used thus far, but costs are decreasing and the next 5–10 years will likely demonstrate whether rarer polymorphisms are also involved in non-Mendelian inherited diseases and predispositions.

When it is determined that a complex disease has familial aggregation, it is important to take into account that families may also share environmental or social factors that predispose to the disease of interest, and therefore the entire impact may not be genetic. One example would be radon gas present in a neighborhood leading to an increased incidence of lung cancer in families living in close proximity. While it may be assumed that the genetic impact is responsible for the development of the disease, environmental exposure is the likely source. Twin studies and adoption studies are utilized to attempt to determine the relative weight of genetics and environment in the development of a certain disease.

1.4 Genetic and Genomic Studies in Critical Care

Genomic medicine and the concept that an individual's genetic makeup may influence not only the severity of and outcome from their critical illness but also their response to the therapies have begun to make their way into the intensive care unit. This section will highlight studies involving analysis of gene expression and genetic association studies in patients with critical illness. While it may appear that advances have been made in the field, it is important to understand that we are not yet in the age of personalized medicine and much work needs to be done.

1.4.1 Genomics Studies in the ICU

With the advent of the DNA microarray technology, gene expression patterns in thousands of genes can lead to insight into disease pathogenesis, treatment, and outcome.

The expression of specific genes in many cases represents the body's specific and complex response to environmental stimuli, such as in the case of a severe infection, trauma, or cardiopulmonary bypass. Examining gene expression may provide a clue as to which genes are important in a specific critical illness. Many studies have examined gene expression in critically ill patients, but most examine the expression of only a few genes. With the advent of the gene expression microarray technology discussed above, investigators have begun to explore gene expression patterns across the genome in children with septic shock using mRNA isolated from whole blood representing the gene expression response in circulating white blood cells. These studies have compared gene expression from blood samples obtained within 1 day of admission to the ICU with that observed in blood of healthy controls, examined longitudinal changes in gene expression in children with septic shock (days 1 and 3), and compared expression in patients with septic shock to expression in children with sepsis or systemic inflammatory response syndrome (SIRS). Genes that were upregulated, downregulated, or unchanged between the groups were examined. The genes that were upregulated when the septic shock group was compared to healthy controls included genes related to immunity and inflammation as would be expected. Unexpectedly, the study demonstrated that many genes related to zinc biology and zinc homeostasis were downregulated. The significance of this finding was supported by the observation that children who did not survive septic shock had lower serum levels of zinc and the demonstration in a murine model that zinc depletion leads to increased mortality from sepsis. In addition, genes involved in T-cell receptor signaling and antigen

presentation appeared decreased suggesting that septic shock may be associated with depression of the adaptive immune system. Interestingly, expression studies of adults with sepsis and septic shock did not identify a downregulation of genes related to zinc biology, although upregulation of genes related to immunity and inflammation and downregulation of genes related to the adaptive immune system was observed.

Gene expression has also been used to identify subgroups of children with septic shock. When a heterogeneous group can be divided into subgroups that are distinguished by differences in the underlying pathophysiology, these subgroups are often called subphenotypes or endotypes. Using genome-wide gene expression profiling from whole blood (which measures the levels of all mRNA transcripts, also referred to as the transcriptome), pediatric septic shock has been demonstrated to encompass two distinct endotypes. These two septic shock endotypes differ in outcomes and reveal differences between endotypes in the underlying biology of septic shock. Endotype A has a higher rate of mortality, and lower expression of genes of the adaptive immune system and the glucocorticoid receptor signaling pathway, compared to endotype B. Interestingly, these septic shock endotypes can be distinguished by the expression of 100 genes, suggesting that a clinically feasible gene expression-based subclassification strategy for septic shock may not be far off.

It is important to note that the septic shock endotypes described above are not primarily intended to estimate the risk of mortality from sepsis. Rather, the primary intent of the endotyping strategies was to subgroup patients based on biological commonalities, which can potentially be targeted with existing or new therapies, such that patients with endotypes that are most likely to benefit are targeted for treatment. The fact that the reported endotypes have differences in outcome adds to the potential clinical relevance of the endotyping strategies.

Genome-wide gene expression microarrays have also been used to investigate the expression profile of adults with ARDS. Although the studies done thus far are relatively small (3–31 patients with ARDS), they have increased our understanding of ARDS and identified potential new biomarkers for ARDS. mRNA for pre-B-cell colony-enhancing factor (PBEF), a cytokine that is involved in the maturation of B-cell precursors, inhibition of neutrophil apoptosis, and perhaps regulation of endothelial cell calcium-dependent cytoskeletal arrangement, was noted to be significantly increased in cells from bronchoalveolar lavage from adults with ARDS, a finding that was also consistent in both a canine and mouse model of acute lung injury. In addition to the elevated mRNA levels, PBEF protein in bronchoalveolar lavage fluid was also elevated in adults with ARDS. Elafin, a potent neutrophil elastase inhibitor, was identified as the gene with the highest fold change in expression when comparing blood samples from patients during the acute and recovery phase of ARDS. Subsequent examination of plasma elafin levels in two different cohorts demonstrated that levels were significantly lower in the acute phase compared to the recovery phase, the same trend as had been observed in gene expression.

A number of studies have compared the gene expression profile from whole blood of patients with sepsis and ARDS to that of patients having sepsis without ARDS. Expression of genes related to neutrophil-related processes were elevated in the patients with ARDS, but were not explained by differences in circulating neutrophil counts, suggesting that the expression of the proteins encoded by these genes are increased in neutrophils of patients with ARDS. In addition, genes related to cell cycle processes were higher in those with ARDS. Since the patients with ARDS generally had a higher

severity of illness, it is still unclear whether these differences in gene expression specifically relate to ARDS. In another study, a comparison of expression of interferon-stimulated genes (ISG) could be grouped into low, middle, and high expression levels; individuals with either high or low expression had fewer ventilator-free days and higher mortality.

1.4.2 Genetic Predisposition in the ICU

As described above, a large amount of genetic variability exists throughout our genome. Whether these differences influence the susceptibility to or outcome from diseases in the critical care setting is an area receiving a great deal of interest. Perhaps the greatest amount of focus of genetic association studies on critical illnesses is in sepsis and ARDS. The general approach has been to do genetic associations studies comparing the frequencies of polymorphisms in a cohort of patients with sepsis (or ARDS) and an at-risk cohort without sepsis (or ARDS). A few genome-wide association studies (GWAS) have been done in patients with sepsis or ARDS. This section will review some of these studies.

1.4.3 Influence of Genetic Variation in Patients with Sepsis

Individual variability in the susceptibility to and outcome from critical care diseases has long been observed, and advances in genomic medicine now give an opportunity to understand these differences.

Individual variability in the susceptibility to and outcome from sepsis and lung injury has long been observed in critically ill patients. Why one child with pneumococcal pneumonia has little consequence of their infection and can be treated as an outpatient while another child develops refractory septic shock and respiratory failure has been attributed to a number of factors. These factors have included virulence of the pathogen, length of time between onset of symptoms and appropriate treatment, and comorbid conditions. While all these factors certainly contribute to the severity of disease, a growing body of evidence suggests that genetic variations in the individual patient may also contribute to the severity of, and outcome from, critical disease. These genetic polymorphisms may not be of any consequence during normal healthy periods, but their importance may become evident only during a severe stressor, such as an infection, trauma, cardiopulmonary bypass, or other scenarios seen in the intensive care unit. A strong genetic influence on the outcome from infections was indicated by a family-based study of adoptees. Adoptees with a biological parent who died due to infection before the age of 50 had a relative risk of death due to an infection of 5.81 (CI = 2.47–13.7); a higher relative risk than that seen when risk related to early death of a biologic parent due to cardiovascular and cerebrovascular disease (4.52; 1.32–15.4) or cancer (1.19; 0.16–8.99) was examined. Thus, an individual's genetic makeup may influence the severity of disease in infection and sepsis.

Genetic variations that lead to alterations in the amount or functional activity of any of the proteins involved in the recognition of or response to pathogen-associated products may influence the individual's response.

Given the tens of thousands of genes in the human genome and the millions of genetic polymorphisms, on which polymorphisms and in which genes should investigators focus? Either a candidate gene study or genome-wide association study (GWAS) can be performed. In a candidate gene study, the genes selected are those encoding protein products known to be involved in the pathogenesis of disease. In a GWAS, genetic variants across the genome are studied with no preconceived notion as to whether the gene of interest encodes for a protein involved in disease. The advantage of such an approach is that it has the capability to identify variants in genes not yet known to be involved in the disease of interest and thus can increase the understanding of the underlying pathogenesis. GWAS generally require

many hundreds to thousands of patients, while candidate gene association studies can be done with hundreds of patients. Consequently, most genetic association studies done in patients with sepsis or ARDS have used a candidate gene approach.

For sepsis, candidate genes used in genetic association studies include the genes for proteins involved with the pathways by which pathogens lead to the clinical symptoms of sepsis (Table 1.1). The body's response to infections involves recognition of pathogen-associated products followed by an inflammatory response that involves a large number of cellular proteins. Genetic variations that lead to alterations in the amount or functional activity of any of these proteins involved in the recognition of, or response to, pathogen-associated products may influence the individual's response. Variants in many candidate genes have been examined for association with sepsis. Many early studies were done before it was clear how many genetic variants are present in the genome and before the differences between races and ethnicities in LD and frequencies of variants were understood. This is likely part of the explanation as to why different genetic association studies have demonstrated conflicting results. Described below are several examples where there is strong evidence that genetic variants are associated with either susceptibility to sepsis or outcome from sepsis.

Genetic variation in mannose-binding lectin may be an important contributor to difference in the host response to infectious illness observed in children.

An example of the influence of genetic variations in proteins involved in the recognition of pathogens on the severity of infections includes polymorphisms in the genes coding for mannose-binding lectin (MBL), a heterotrimeric protein involved in binding bacterial surface carbohydrates and the opsonization of bacteria. A helical domain in the tertiary structure of the protein is crucial for the formation of the active heterotrimer. Three genetic polymorphisms in the gene coding for MBL result in amino acid changes in the helical tails of the protein and result in increased degradation and decreased serum levels of MBL. Genetic association studies have demonstrated associations between the 3 MBL genetic polymorphisms and increased susceptibility to infections, hospitalizations due to infections, number of acute respiratory infections and risk of meningococcal infections in children, and pneumonia and sepsis in neonates. In adults, these polymorphisms have been associated with recurrent respiratory infections, invasive pneumococcal infections, and viral coinfections with pneumococcal pneumonia.

The family of leukocyte Fcγ receptors is also involved in the recognition of bacteria, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitides*. Fcγ receptors bind the Fc portion of IgG bound to bacteria, thereby facilitating phagocytosis and inducing the inflammatory response. Several polymorphisms have been described in the genes coding for the various Fcγ receptors that alter their binding affinity to the various subclasses of IgG. Two such polymorphisms have been described in the genes coding for the FcγRIIIb receptor and the FcγRIIa receptor. In the case of the FcγRIIIb receptor, the genetic polymorphism results in a four-amino-acid substitution (allotypes FcγRIIIb-NA1 or -NA2) in the receptor that alters the opsonization efficiency. In the case of the FcγRIIa receptor, the genetic polymorphism results in replacing a histidine for an arginine in the extracellular domain of the receptor at amino acid position 131. The variant FcγRIIa receptor containing the histidine binds the Fc region of IgG2 with a lower affinity and results in reduced phagocytosis in vitro compared with the more common FcγRIIa receptor containing the arginine. In association studies, a higher frequency of individuals homozygous for the NA2 allotype of the FcγRIIIb receptor or an arginine at position 131 in the FcγRIIa receptor was found in patients with severe meningococcal disease or fulminant meningococcal sepsis.

Table 1.1 Genetic polymorphisms and risk of infection and sepsis

Gene	Polymorphism[a]	Consequence of polymorphism
MBL	Variant B, C, D	Variants associated with decreased levels and activity and increased risk of infection
FCγRIIa	H131R	R associated with decreased affinity to IgG_2 and opsonization and increased risk of infection and septic shock
CD-14	−159 C/T	T allele associated with increased levels and susceptibility to sepsis and sepsis-related mortality in adults
TNF-α	−308 G/A, −238 G/A, LT-α + 250 G/A	A alleles for each polymorphism are associated with increased TNF-α levels, increased mortality in sepsis and meningococcal disease, increased sepsis in adults with pneumonia, and increased mortality in bacteremia and sepsis
IL-6	−174 G/C	G associated with increased IL-6 levels in patients but C associated with increased levels in monocytes from neonates, sepsis in neonates but not adults, and severe sepsis and organ dysfunction in children
IL-1ra	Variable 86-bp repeat	A2 associated with increased levels of $IL\text{-}1_{RA}$ and variable results of association studies examining risk of sepsis and mortality
IL-10	−1082 G/A, −819 C/T, −592 C/A	GCC haplotype associated with increased levels and sepsis but not mortality
IRAK-1	+1595 T/C	C associated with increased NF-kB translocation and presence of shock and higher 60-day mortality in adults with sepsis
ACE	287 bp I/D	DD associated with increased serum and tissue levels and more severe meningococcal disease in children; no association with sepsis related mortality in neonates or adults
PAI-1	4G/5G	4G associated with increased levels and septic shock in meningococcal disease
Protein C	−1641 A/G and −1654 C/T	AC haplotype associated with increased mortality and organ dysfunction in adults with sepsis and with decreased protein C serum level; GC haplotype associated with more severe sepsis in children less than 1 year of age with meningococcemia

MBL mannose-binding lectin, Ig immunoglobulin, *TNF* tumor necrosis factor, *LT* lymphotoxin, *IL-1ra* interleukin-1 receptor antagonist, *IL-10* interleukin-10, *IRAK-1* interleukin receptor-associated kinase 1, *ACE* angiotensin-converting enzyme, *PAI* plasminogen activator inhibitor

[a]Terminology used for the various polymorphisms are the ones most commonly used in the literature and may refer to the nucleotide position, amino acid position, or name of the allele. This table is representative of polymorphisms examined in sepsis but does not include all such polymorphisms

Loss of homeostatic mechanisms regulating the coagulation/fibrinolytic system also plays an important role in sepsis. Plasminogen activator inhibitor 1 (PAI-1) inhibits fibrinolysis, thereby favoring the formation of microthrombi in the capillaries. The pathophysiology of multiple organ dysfunction syndrome in patients with sepsis is thought to involve, in part, intravascular fibrin deposition. Thus, elevated PAI-1 activity could contribute to organ failure in

sepsis, and elevated plasma concentrations have been observed in patients with sepsis. A genetic variation in the gene coding for PAI-1 consisting of either the presence of 4 guanines or 5 guanines at a specific location appears to influence the amount of PAI-1 produced. Individuals homozygous for the 4G genotype (4G/4G) produce more PAI-1 than individuals homozygous for the 5G genotype (5G/5G) or individuals that are heterozygous (4G/5G). Association studies have demonstrated that children with meningococcal disease who were 4G/4G at this site had an increased risk of death compared to children who were 4G/5G or 5G/5G. More recent studies in both children and adults have demonstrated higher mortality in individuals homozygous for the 4G allele in a number of infectious diseases.

Variants in other candidate genes involved with inflammation and with other aspects of the pathophysiology of sepsis have also been reported to be associated with sepsis. Table 1.1 lists additional selected variants that have been reported to be associated with sepsis using a candidate gene approach. To date, only two GWAS studies have been performed in patients in sepsis with both looking for association of SNPs with death in patients with sepsis. Both were relatively small for GWAS, but in each case, they identified proteins that had not yet been implicated in the pathophysiology of sepsis.

1.4.4 Influence of Genetic Variation on Lung Injury and Acute Respiratory Distress Syndrome

Severe lung injuries in both adults and children can be precipitated by a diverse array of causes and are classified as either direct injury, when the insult is from the alveolar side of the alveolar/capillary membrane, or indirect injury, when the insult is from the capillary side. Major causes of direct lung injury include pneumonia, aspiration, pulmonary contusion, and inhalation, while major causes of indirect injury include sepsis, trauma without pulmonary contusion, cardiopulmonary bypass, and multiple transfusions. Despite these various causes, the central pathogenesis of ARDS involves derangements in multiple biological processes. These include activation of inflammation, loss of coagulation and fibrinolytic homeostasis, disruption of vascular permeability, epithelial and endothelial cell apoptosis as well as proliferation, and derangements in surfactant. Some of these processes, notably inflammation and coagulation, play key roles in the pathophysiology of sepsis as well as ARDS. Thus, it is not surprising to find that the candidate genes examined in genetic association studies for ARDS are in many cases the same as those examined in sepsis (Table 1.2). This section will review some of the genetic variations with the most consistent association with either the development of or outcome from ARDS.

Interleukin-6 (IL-6) is a cytokine with pleiotropic effects that is released in response to infection or injury and impacts host defense in part through its effect on stimulating the synthesis of acute phase proteins and on specific subgroups of T cells. Increased levels of IL-6 are found in plasma and bronchoalveolar lavage fluid in patients with ARDS and are associated with outcome. Genetic variants and haplotypes in IL-6 promoter have been shown to be associated with plasma levels of IL-6 and with development of ARDS. One explanation for why these haplotypes are associated with ARDS would be if they are associated with differences in the levels of IL-6.

As discussed previously, expression microarrays have been invaluable in identifying other potential mediators involved in the pathophysiology of lung injury. The expression of pre-B-cell colony-enhancing factor (PBEF) was

Table 1.2 Genetic association in studies of acute lung injury or ARDS

Gene	Polymorphism[a]	Consequence of polymorphism
SP-B	−1580 T/C and intron 4 dinucleotide repeats	C allele and dinucleotide variants associated with ARDS and need for mechanical ventilation
MBL	Variant B, C, D	B variants associated with increased susceptibility to ARDS; greater organ dysfunction and higher mortality in patients with ARDS
PBEF	−1001 T/G, −1543 C/T	−1001 G/−1543 C haplotype associated with a higher risk of ARDS
TNF-α	−308 G/A	−308 A allele associated with increased mortality in adults with ARDS
IL-6	Haplotypes	Specific IL-6 haplotypes are associated with ARDS
NRF2	−617 C/A	A allele associated with lower transcription and increased risk of ARDS in adult trauma patients
NFκBIA	−881 A/G, −826 C/T, −297 C/T	−881 G/−826 T/−297 C haplotype associated with increased risk of ARDS
IL-10	−1082 G/A, −819 C/T, −592 C/A	−1082 GG associated with higher IL-10 levels, increased risk for development of ARDS, and lower mortality and organ failure in adults with ARDS
ACE	I/D	DD associated with increased susceptibility to and outcome from ARDS
MLCK	Multiple SNPs and haplotypes	Several SNPs and haplotypes associated with both sepsis and sepsis-induced or trauma-induced ARDS

SP-B surfactant protein B, *MBL* mannose-binding lectin, *PBEF* pre-B-cell colony-enhancing factor, *TNF* tumor necrosis factor, *IL-6* interleukin-6, *NRF2* NF-E2 related factor 2, *NF-κBIA* nuclear factor-kappa inhibitor A, IL-10 interleukin-10, *ACE* angiotensin-converting enzyme, *MLCK* myosin light chain kinase

[a]Terminologies used for the various polymorphisms are the ones most commonly used in the literature and may refer to the nucleotide position, amino acid position, or name of the allele. This table is representative of polymorphisms examined in sepsis but does not include all such polymorphisms

found to be significantly elevated in both animal and human studies of ARDS using this approach. PBEF is a lesser studied cytokine involved in the maturation of B-cells, inhibition of neutrophil apoptosis, and perhaps regulation of the endothelial cell calcium-dependent cytoskeletal arrangement. Two genetic polymorphisms have been identified in the promoter region, −1001 T/G and −1543 C/T which appear to influence the development of ARDS. Carriers of the G allele at position −1001 had a 2.75-fold increased risk of ARDS, and the G allele remained an independent risk factor after controlling for several other variables. The T allele at position −1543 was found at a lower frequency in adults with ARDS. Combining these two polymorphisms in a haplotype analysis demonstrated that adults with the −1001 G/ −1543 C haplotype had a higher risk of ARDS (7.7-fold). The consequence of these two polymorphisms remains to be elucidated, though the −1543 T allele may result in reduced expression.

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Deficiency in, or impaired activity of surfactant protein B appears to play a role in a number of interstitial pulmonary diseases in humans including ARDS.

Pulmonary surfactant is synthesized by the type II alveolar epithelial cells and is required for normal lung function. One of surfactant's primary functions is to lower the surface tension at the alveolar air-liquid interface. Surfactant is composed of phospholipids and four proteins, surfactant protein (SP)-A, SP-B, SP-C, and SP-D. Knockout models in mice have demonstrated that of these four proteins, only SP-B is absolutely required for postnatal survival. Deficiency in or impaired activity of SP-B appears responsible for a number of interstitial pulmonary diseases in humans, including ARDS. Several genetic variations exist in the genes coding for the surfactant proteins, and two will be discussed here: the SP-B + 1580 T/C polymorphism and insertion/deletion polymorphism consisting of dinucleotide (CA) tandem repeats in intron 4. Several studies have demonstrated an association between these polymorphisms and the need for mechanical ventilation in children (SP-B + 1580 T/C) and mechanical ventilation and ARDS in adults (SP-B + 1580 T/C polymorphism and insertion/deletion of dinucleotide (CA) tandem repeats). The consequences of these variations are not fully known. The SP-B + 1580 T/C polymorphism results in an amino acid change in exon 4 in a region of the amino terminal propeptide, which is thought to play a role in targeting of SP-B to lamellar bodies. The resulting amino acid change alters glycosylation of SP-B and may affect the level of SP-B by altering its processing or stability. Aberrant proteolytic processing of the SP-B product encoded by the C allele is supported by a recent report, demonstrating that the C allele is associated with the absence of a specific pro-SP-B cleavage product in neonates. The intron 4 dinucleotide repeat length variation polymorphism is associated with incompletely spliced SP-B mRNA. Interestingly, in Caucasians this length variation polymorphism in intron 4 is in linkage disequilibrium with the SP-B + 1580 T/C polymorphism; the C allele is associated with the deletion variant at the intron 4 polymorphic site. Further, work is needed to not only define the consequence of these genetic variations on surfactant function but also to further evaluate whether these genetic variations influence the development of ARDS.

Angiotensin-converting enzyme (ACE) may also have a role in lung injury. ACE is present in pulmonary endothelium and is responsible for converting angiotensin I (ATI) to ATII. ACE levels are elevated in the bronchoalveolar lavage fluid of adults with ARDS, and higher levels are associated with mortality from ARDS. The key component is most likely ATII, which has apoptotic effects on alveolar epithelial and endothelial cells in vitro. ATII receptor antagonists block pneumocyte apoptosis in a model of meconium aspiration. Another important component of this system is ACE2, a homolog of ACE expressed in human lungs, which is a negative regulator of the renin-angiotensin system as well as the probable receptor for the SARS virus in humans. Lung injury models using knockout mice lacking the ACE2 gene have higher ATII levels and exaggerated lung injury compared to wild-type mice. However, the lung injury is reversed if the ACE gene is inactivated in the ACE2 knockout mice. This suggests that ACE induces lung injury through ATII and that ACE2 protects against lung injury. Indeed, ACE inhibitors and ATII antagonists appear to decrease the severity of lung injury in animal models and the risk of aspiration pneumonia in some adult populations, and reduce the 30-day mortality in adults with pneumonia. Several studies have demonstrated the ACE D/D genotype is associated with the susceptibility to and outcome from ARDS (Table 1.2).

More recently, GWAS and exome sequencing have been used to identify genetic variants that may be associated with ARDS. As discussed above, because GWAS require a large number of patients, those done using ARDS

patients have limited power to detect associations. Only two GWAS on ARDS have been done thus far. The first in trauma patients did not identify any variant that reached the significance threshold. The second, done very recently, used several new analytic tools to analyze the results and found several SNPs associated with ARDS. These were in genes encoding for proteins not known to be involved in the pathophysiology of ARDS. One of these variants was in the gene for the P-selectin ligand and changed one of the amino acids in the protein. Using animal models, P-selectin was implicated in ARDS pathophysiology. Further studies will be required to determine if the P-selectin ligand is involved in ARDS in patients. Lastly, an exome sequencing study, in which all the exons encoding for proteins were sequenced, has been done on ARDS patients and identified variants in two genes not previously implicated as playing a role in ARDS pathophysiology, the X-linked gene arylsulfatase, and the XK Kell blood group complex member 3 gene. Future studies will be needed to determine if these genes are involved in ARDS.

1.4.5 Other Potential Areas of Interest in Genetic Variation in the ICU

Genetic polymorphisms in genes coding for proteins involved in coagulation and fibrinolysis may be very important in the risk of bleeding and thrombosis in critically ill children.

Two other areas should be mentioned with regard to the influence of genetic variations in the ICU. The first is in the area of coagulation. Several examples of genetic polymorphisms in genes coding for proteins involved in coagulation and fibrinolysis were discussed above in relation to sepsis and ARDS. However, these and many other genetic variations that exist in other components of the coagulation cascade could also influence the development of thrombosis, including deep venous thrombosis in critically ill patients. Thrombosis of central venous catheters is a recurring problem in ICUs, and while certain environmental factors play a role (e.g., length of time catheter is in place, size of the patient and vessel), genetic polymorphisms in the patient favoring the formation of thrombi may also play a role.

The area of pharmacogenomics attempts to determine the influence of genetic variations in genes affecting the various aspects of drug action.

Finally, the action of every drug that is used in the ICU can potentially be influenced by genetic variation in the patient. Such medications include inhaled β_2-agonists, or the array of intravenous vasoactive agents, sedatives, muscle relaxants, antibiotics, steroids, etc. All bind to protein receptors and either activate or block specific signal transduction pathways, many bind protein carriers or transporters, and most are metabolized by various protein enzymes. Every gene coding for each of these proteins has multiple genetic variations with the potential to influence the levels or activities of these proteins. The area of pharmacogenomics attempts to determine the influence of genetic variations in genes affecting these various aspects of drug action. However, while the list of genetic polymorphisms in genes affecting drug action is growing rapidly, there are few clinical examples of the degree of influence that these genetic variations have on the response to drugs in the ICU. For example, warfarin is the most widely used oral anticoagulant for long-term prophylaxis and treatment of thromboembolic disorders and is used in many children and adults with mechanical valves. The metabolism of and response to warfarin involves several enzymes, two of which exhibit genetic variations that dramatically alter the levels of warfarin. For one of these genes, CYP2C9, the common allele is referred to as CYP2C9*1 and is consider the wild-type, while CYP2C9*2 contains a C to T nucleotide change at position 430 in exon 3 and CYP2C9*3 contains an A to C nucleotide change in exon 7. CYP2C9*2 has approximately 80% of the metabolic activity of the wild-type CYP2C9*1, while CYP2C9*3 contains only 20% of the wild-type activity. By also using genetic variation in

a second gene, vitamin K epoxide reductase complex subunit 1 or VKORC1, one can account for more than 50% of the observed dosing variability. Current practice in the use of warfarin usually involves starting at an age and weight specific dose and monitoring coagulation studies. However, because of the genetic variations in these two enzymes and perhaps others, different patients take different amounts of time to achieve the appropriate therapeutic dose. Knowing the specific genotypes of patients prior to initiating warfarin may allow for more appropriate dose selection, less time to achieve therapeutic levels, and less risk of adverse events. Recently, an algorithm using the patient's genotypes at these two sites has been developed that allows for more accurate dosing in some populations. Although these algorithms are being developed and tested, it should be kept in mind that they do not account for drug-drug interactions.

1.5 Conclusion

The era of the study of the genetic impact on critical illness in children is present. Clinicians must be prepared to deal with the growing body of literature related to genetic and genomic influence on critical disease development, treatment, and outcome and be able to critically review the literature in order to determine the impact on the patients they are caring for daily. For the results of these representative genetic association studies to make the leap into clinically impacting care, they must meet certain criteria. First and foremost, the phenotype must be well defined; that is, the enrolling patients with ARDS or sepsis must meet strict and well-accepted criteria. Second, they must be high-quality studies, utilizing highly sensitive and specific methods for genotyping. Third, the studies must use a large sample size or replication cohorts to assure that no type I or type II errors are made based simply upon the number of individuals studied. Finally, the impact of the genetic variant on the protein product must possess biologic plausibility as impacting the development or the outcome of the disease of study. It is likely that the results of genomic and genetic studies will initially be used to stratify critically ill patients into subgroups to determine if such subgroups respond differently to treatment. Only after studies demonstrate an impact of genomics or genetics on outcome is it likely that tailoring therapy based on subgrouping patients using genetics or genomics will be used to more precisely target treatment to the individual patient.

Review Questions

1. Which part of the gene encodes for the actual amino acid sequence of proteins?
   A. Alleles
   B. Codons
   C. Exons
   D. Introns
   E. Promoter regions

2. A new fast-acting anticonvulsant is produced that is superior to anything currently known. This new anticonvulsant's mechanism of action involves its conversion to an active metabolite by enzyme A in the bloodstream and the binding of this metabolite to a specific receptor in the brain coded for by gene B. After several doses, the child continues to have seizures. You hypothesize that your patient may have a genetic variation either within the gene coding

for enzyme A, which results in your patient being unable to convert the drug to the active metabolite, or in gene B coding for receptor, such that the active metabolite cannot bind. Which of the following describes the best approach to test your hypothesis? Your budget is limited and there is no way to measure the active metabolite.

A. Perform whole genome sequencing.
B. Isolate mRNA from whole blood and use polymerase chain reaction technology targeting genes A and B to identify and quantify amounts of mRNA transcribed.
C. Perform a transcriptional microarray to examine whether genes A and B are being transcribed.
D. Isolate DNA from your patient and sequence genes A and B.
E. Isolate DNA from a brain biopsy and sequence gene B coding for the receptor.

3. Which of the following statements regarding genetic mutations is most accurate?
   A. Germline mutations which occur in reproductive cells are the only mutations of clinical consequence.
   B. Mutations in the intron/exon boundary region are of no clinical significance because they are excised during the process of splicing.
   C. Mutations in the noncoding regulatory regions may alter the quantity of mRNA transcribed, but do not affect the expression of the gene.
   D. Mutations that occur in the coding regions of the gene may have several consequences, including no effect at all on the end product protein.
   E. Translocations are large-scale mutations that entail switching of chromosomal regions between different loci on the same chromosome.

4. You are caring for two brothers with acute respiratory distress syndrome secondary to smoke inhalation from an apartment fire. These two infants were apparently sleeping in the same crib when they were rescued simultaneously by fire fighters. The first infant was extubated within 48 h of intubation and is doing well with a minimal oxygen requirement. The second remains intubated on high-frequency oscillatory ventilation. In attempting to understand the difference in their clinical response to the seemingly identical insult, you suspect that it may be related to a polymorphism in one of the genes that codes for surfactant protein B. In considering this possibility, which of the following is true?
   A. Although plausible, it is unlikely to be associated with a polymorphism because polymorphisms are rare occurring in less than 1% of the population.
   B. It is not plausible because variances in the translation of such a complex protein require differences in an entire haplotype, and not simply a single-nucleotide polymorphism.
   C. It is plausible because genetic polymorphisms may influence the quantity of mRNA transcribed and/or the functional activity of the surfactant protein B.
   D. It is unlikely as there are no reports of associations between surfactant protein gene polymorphisms and outcomes from pulmonary disease.
   E. It is unlikely because dysfunctional surfactant protein B demonstrates an X-linked pattern of inheritance.

5. A patient of yours has severe ARDS with pneumococcal pneumonia. You do not observe any variant in the genes for surfactant A, B, C, or D, but you do identify a novel variant in gene Z, which codes for a protein involved in sur-

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factant production. The variant lies in an intron but in a splice junction between an exon and an intron. Which of the following is most accurate?

A. The variant could account for the phenotype as it is in a highly conserved area of the gene, and the nucleotide change could result in a significant amino acid change.
B. The mutation could not account for the phenotype because it is in an intron and does not involve coding sequences.
C. The mutation could not account for the phenotype because it is not in a gene coding for surfactant A, B, C, or D.
D. The variant could not account for the phenotype because it would be spliced out of the final transcript.
E. The variant could account for the phenotype by altering the splicing of the primary transcript and creating a nonfunctional protein.

Answers

1. C
2. D
3. D
4. C
5. E

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Oxygen Delivery and Oxygen Consumption in Pediatric Critical Care

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Contents

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Learning Objectives

- Describe metabolic pathways (glycolysis, Krebs cycle, electron transport, oxidative phosphorylation) that are essential to cellular respiration.
- Define the factors that determine the arterial oxygen content.
- Detail how to calculate oxygen delivery.
- Demonstrate the interdependence of the lungs, heart, and blood on peripheral oxygen delivery.
- Describe the mechanisms for the measurement of oxygen consumption.
- Describe the variables that can influence oxygen consumption in critically ill children.
- Define the use of and limitations of the Fick equation in the evaluation of the adequacy of oxygen delivery.
- Define the oxygen extraction ratio; describe how it varies with regional demands and disease states.
- Describe the difference between aerobic and anaerobic metabolism.
- Describe what ATP and NADP really do.
- Describe the biochemical (laboratory) evaluation of the adequacy of circulatory function.

2.1 Introduction

Every cell in an aerobic multicellular organism needs a system to receive oxygen and dispose of waste. This process presents unique challenges to each organism. The fact that animals as big as blue whales and as small as hummingbirds, under widely diverse conditions, evolve mechanisms to ensure adequate oxygen delivery is one of the most fascinating topics in physiology. In addition, organisms must maintain oxygen delivery during pathologic stress states that can include infection, injury, intoxication, and metabolic abnormalities.

The maintenance of adequate oxygen delivery to meet the demands of the tissues is the essence of critical care medicine.

Maintaining an adequate oxygen delivery to meet the demands of organs and tissues is a fundamental task in critical care medicine. Inadequate oxygen delivery, which can occur on a global level as in cardiogenic shock or on a regional level such as traumatic brain injury, must be recognized and treated in order to achieve optimal outcomes. Therefore, an understanding of the determinants of oxygen delivery and oxygen consumption in the critically ill pediatric patient is essential for any pediatric critical care clinician.

Molecular oxygen moves down a concentration gradient from the atmosphere to the blood, and from there to the cell and into the mitochondria. Ultimately, oxygen will be used not only in cellular respiration as the final step in the energy production from carbohydrates, fats, and protein but also in several oxidative reactions unrelated to energy. This chapter reviews oxygen-related biochemical processes, their alterations in critical illness, and the various methods for measuring oxygen delivery and consumption.

2.2 Biochemical Basis

All tissues need energy to maintain their biological processes. This energy is provided by a series of biochemical oxidation/reduction reactions. Oxidation refers to the process in which a molecule, not necessarily involving oxygen, loses electrons. Reduction is the reverse process in which a molecule gains electrons.

In oxidation reactions, the electron moves down an energy gradient, releasing energy with every oxidation/reduction cycle. A portion of this energy is captured in reduction reactions by certain molecules, such as adenosine triphosphate (ATP), that become reservoirs of energy. ATP is the most important

energy storage/supply molecule because of two key properties. First, the two outer bonds between the three phosphate groups have a very high latent or intrinsic energy, many times more than that of most chemical bonds. This energy is liberated when the bond is broken. Second, these "high-energy" bonds are very unstable and can easily break down, making such energy readily available. ATP is constantly being used and regenerated; in fact, the rotatory machine at the core of the ATP-synthase can rotate hundreds of times per second, and the number of protons going through all the mitochondria in the cells of the human body every second is approximately equivalent to the number of stars in the known universe – for a fascinating discussion of the energy considerations of cellular metabolism, see "The Vital Question" by Nick Lane.

ATP is the main energy carrier in the cellular system. The high-energy molecules nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH) are also essential to the energy-generating processes of the cell because they donate electrons to an electron transport system that results in the production of ATP. The phosphorylation of ATP is a reduction reaction, with a net increase in stored energy. Dephosphorylation, such as the transformation of ATP into ADP, releases energy. Although part of this released energy is dissipated as heat, much of it is used to generate the work needed for normal cellular function (e.g., maintaining a sodium gradient across a biological membrane).

Cellular respiration occurs in three stages (◘ Fig. 2.1). The first step is *glycolysis*, during which one molecule of glucose is converted into two molecules of pyruvate with the net production of two ATP molecules and two NADH molecules. This first step is anaerobic; it does not require oxygen and occurs in the cytoplasm of the cells.

Pyruvate metabolism is a reaction that links glycolysis with the second step, the Krebs cycle. Under aerobic conditions, pyruvate metabolism consists of the conversion of pyruvate into acetyl-CoA while NAD + is reduced to NADH. Acetyl-CoA enters the Krebs cycle where the oxidation process continues. Amino acids from protein breakdown also enter the Krebs cycle by conversion to pyruvic acid or acetyl-CoA. Lipid metabolism generates glycerol and fatty acids that enter the Krebs cycle as metabolites of glycolysis or as acetyl-CoA.

The *Krebs cycle*, which occurs in the mitochondria, is illustrated in a simplified form in ◘ Fig. 2.2. For the two molecules of acetyl-CoA that enter the Krebs cycle (from one molecule of glucose), two ATP molecules, six NADH molecules, and two FADH molecules are produced, while four molecules of carbon dioxide are released. Although two ATP molecules are produced, the true energy gain from the Krebs cycle is generated from the NADH and FADH molecules.

NADH and FADH undergo redox reactions that cause the sequential transfer of electrons down the *electron transport chain*. The transfer of electrons causes a hydrogen gradient to develop across the inner mitochondrial membrane. These redox reactions are facilitated by a series of protein complexes (I, II, II, and IV), ubiquinone (Q), and cytochrome c. The transfer of electrons down the electron transport chain terminates with the activation of ATP synthase (ATPS). Activated ATP synthase leads to *oxidative phosphorylation* as oxygen serves as the final electron donor. Oxygen is reduced to water and an excess of 30 molecules of ATP are produced.

For the Krebs cycle, electron transport, and oxidative phosphorylation to occur with efficient production of energy, oxygen must be present. Under anaerobic conditions, the final electron acceptor can be a metabolite, such as pyruvate that will conserve some of the latent energy. The anaerobic pathway is far less efficient than the aerobic process in producing energy. Anaerobic metabolism cannot support the functioning of most tissues for extended peri-

Energy from nutrition is extracted and stored in ATP in three stages. The first step, glycolysis, is anaerobic. A linking reaction results in the conversion of pyruvate to acetyl-CoA that then enters the Krebs cycle (second step). In the third stage of the process, molecules of NADH and FADH from the Krebs cycle enter the electron transport chain and facilitate a cascade of electron transfers resulting in the activation of ATP synthase.

Activated ATP synthase catalyzes oxidative phosphorylation. Oxygen is reduced to water and an excess of 30 molecules of ATP are produced.

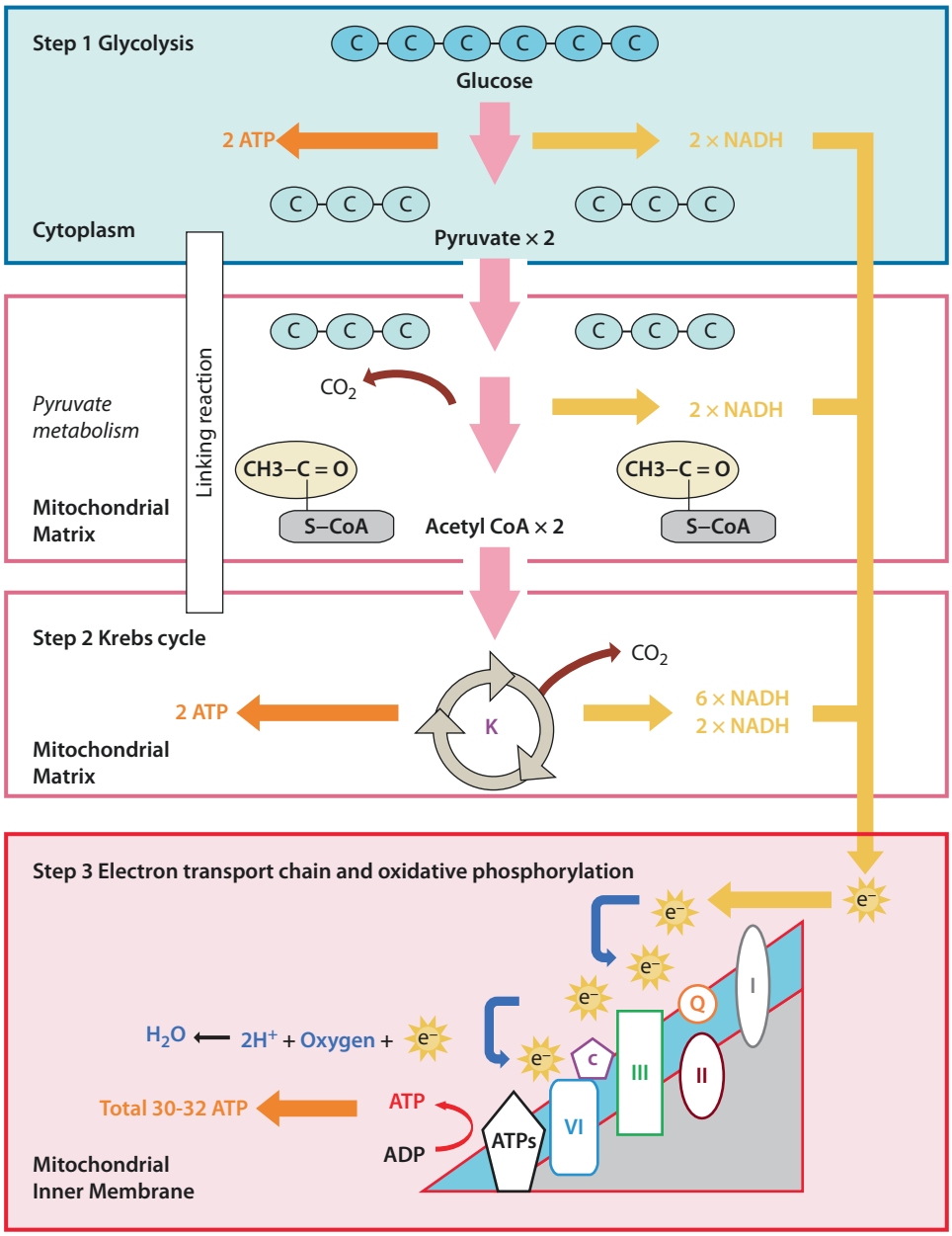


Fig. 2.1 Overview of cellular respiration. (Courtesy of F. Maffei)

In the absence of oxygen, elevation of lactate levels and accumulation of H^+ result in metabolic acidosis.

ods, particularly those with high-energy demands, such as the brain or the heart. If oxygen is not present, pyruvate cannot enter the Krebs cycle, and instead, it is converted into lactate resulting in elevations of blood lactate levels. Therefore, an elevated plasma lactate level can be used as an indicator of anaerobic metabolism and insufficient oxygen delivery. When oxygen becomes available, most of the lactate will rapidly be reconverted to pyruvate and subsequently enter the Krebs cycle. Most of this reconversion occurs in the liver.

Elevation of blood lactate may occur in the absence of tissue hypoxia. Inflammatory mediators, catecholamines, and other factors, which may stimulate Na/K adenosine triphosphatase activity, can produce elevated lactate. This is commonly referred to as type B lactic acidosis. In addition, a decrease in lactate clearance can produce elevated blood lactate levels. This has been found to occur in the presence of hepatic insufficiency and with severe sepsis.

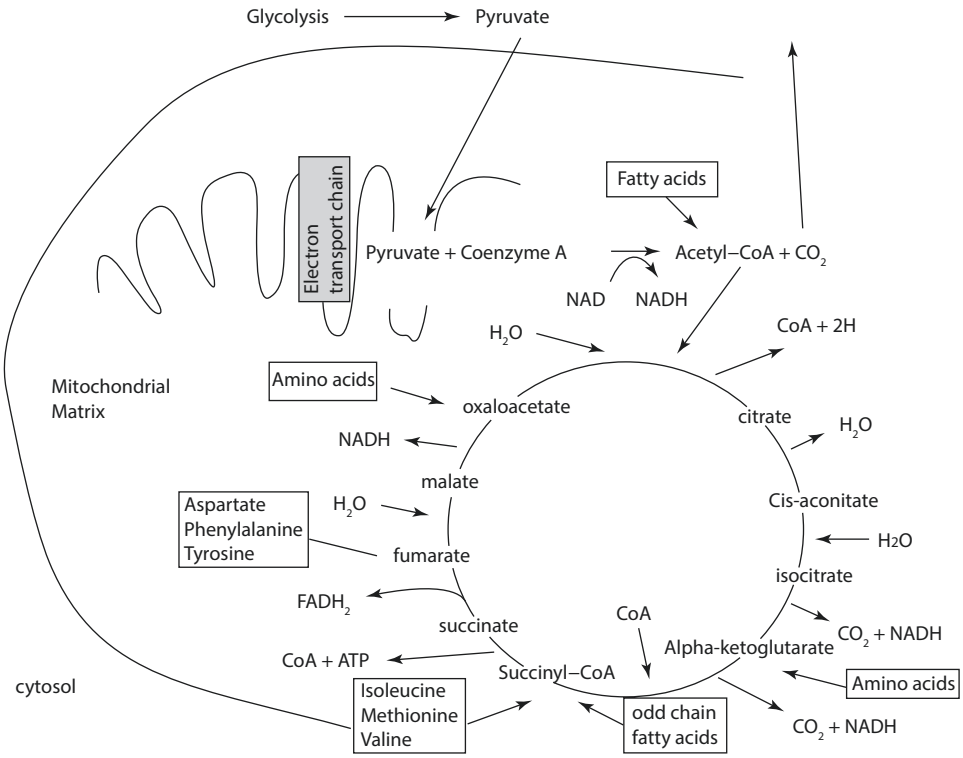


Fig. 2.2 The Krebs cycle

Lactate elevation is not the primary contributor to the metabolic acidosis seen during tissue hypoxia. A second biochemical process that occurs in the setting of hypoxia is the accumulation of hydrogen ions. These hydrogen ions diffuse out of the cell because oxygen is not available to be the final acceptor of hydrogen. The primary mechanism of hypoxic acidosis is not the accumulation of lactate, but rather the accumulation of unused hydrogen ions.

As noted, the acidosis that accompanies anaerobic metabolism is primarily intracellular. This concept is particularly important as it relates to therapy. The intravenous administration of sodium bicarbonate can correct the extracellular acidosis, but because bicarbonate is not readily diffusible, it will only slowly correct intracellular acidosis. The rapid infusion of bicarbonate may worsen intracellular acidosis. With rapid infusion of sodium bicarbonate, there will be a significant increase in blood levels of carbon dioxide, liberated from the dissociation of carbonic acid formed when bicarbonate ion buffers extracellular hydrogen ion. Carbon dioxide readily diffuses into cells, where it associates with water to reform carbonic acid, thereby worsening the intracellular acidosis. Therefore, the routine use of sodium bicarbonate to correct the hypoxic acidosis may be deleterious. As such, the ideal treatment for acidosis associated with anaerobic metabolism is to *improve oxygen delivery*.

The use of sodium bicarbonate to correct hypoxic acidosis may be deleterious. The ideal treatment for acidosis associated with anaerobic metabolism is to improve oxygen delivery.

There are certain clinical circumstances where the use of sodium bicarbonate may improve oxygen delivery. Profound extracellular acidosis may adversely affect myocardial function and the response to catecholamines; therefore, sodium bicarbonate may improve cardiac function, increase the cardiac output, and, thus, increase oxygen delivery. Sodium bicarbonate may also be useful when hypoxia is secondary to severe pulmonary hypertension. Acidosis increases pulmonary vascular resistance. The administration of sodium bicarbonate may ameliorate pulmonary vasoconstriction, thus improving oxygenation.

2

2.3 Oxygen Delivery

In order to appreciate the factors that influence the delivery and utilization of oxygen, it is necessary to have a clear understanding of the terms used to describe this process. These definitions include the following:

Oxygen delivery (DO_2) The rate of oxygen delivered per unit of time to a tissue, an organ, or the entire body.

Oxygen consumption (VO_2) The oxygen utilized per unit of time by a tissue, an organ, or the entire body.

Oxygen extraction (O_2ER) The fraction of the oxygen delivered in the blood that is utilized or consumed by a tissue, an organ, or the entire body of patient.

Oxygen demand A theoretical concept describing the amount of oxygen that a tissue, an organ, or the entire patient's body would need to consume to meet all its needs under a given set of circumstances.

Oxygen demand cannot be measured, but it is a useful concept when reflecting upon the factors which affect oxygen delivery and consumption.

When oxygen demands are being met, further increases in oxygen delivery will have no effect on oxygen consumption.

Oxygen debt The difference between oxygen delivery and the estimated oxygen demand. Theoretically, when there is a significant oxygen debt, increases in oxygen delivery will increase oxygen consumption. Alternatively, when oxygen demands are being met (no oxygen debt), further increases in oxygen delivery will have no effect on oxygen consumption.

The global delivery of oxygen throughout the body (DO_2) is defined as the product of the oxygen content of the arterial blood (CaO_2; in mL/dL) and the blood flow or cardiac output (CO; in L/min) as expressed in the following equation:

$$\text{Oxygen delivery} = \text{CO} \times \text{arterial}\,\text{O}_2\,\text{content}$$

$$\text{DO}_2 = \text{CO} \times \text{CaO}_2$$

$$\text{DO}_2\,(\text{mL/min}) = \text{CO}\,(\text{L/min}) \times \text{CaO}_2\,(\text{mL/dL})$$

This equation is multiplied by 10 to convert the units into mL/min:

$$\text{DO}_2 = 1000\,\text{mL/min or } 550-650\,\text{mL/min/m}^2 \text{ if CI used}$$

There are several determinants of the cardiac output and CaO_2. Each can become deranged in critically ill patients (Fig. 2.3). Identification of the primary derangement and the initiation of appropriate directed therapies are required to achieve physiologic stability. The determinants of oxygen delivery are arterial oxygen content and cardiac output. Each will be discussed in detail.

2.3.1 Arterial Oxygen Content

The arterial oxygen content is the sum of the oxygen bound to hemoglobin and the oxygen dissolved in the blood. Most of the oxygen in blood travels bound to hemoglobin; only a minimal amount is present as dissolved oxygen. Therefore, the oxygen content depends primarily on the oxyhemoglobin saturation and the hemoglobin concentration. The formula for the calculation of arterial oxygen content is:

$$\text{CaO}_2 = \text{Hgb} \times 1.34 \times \text{SaO}_2 + \text{PaO}_2 \times 0.003$$

The individual variables are as follows:

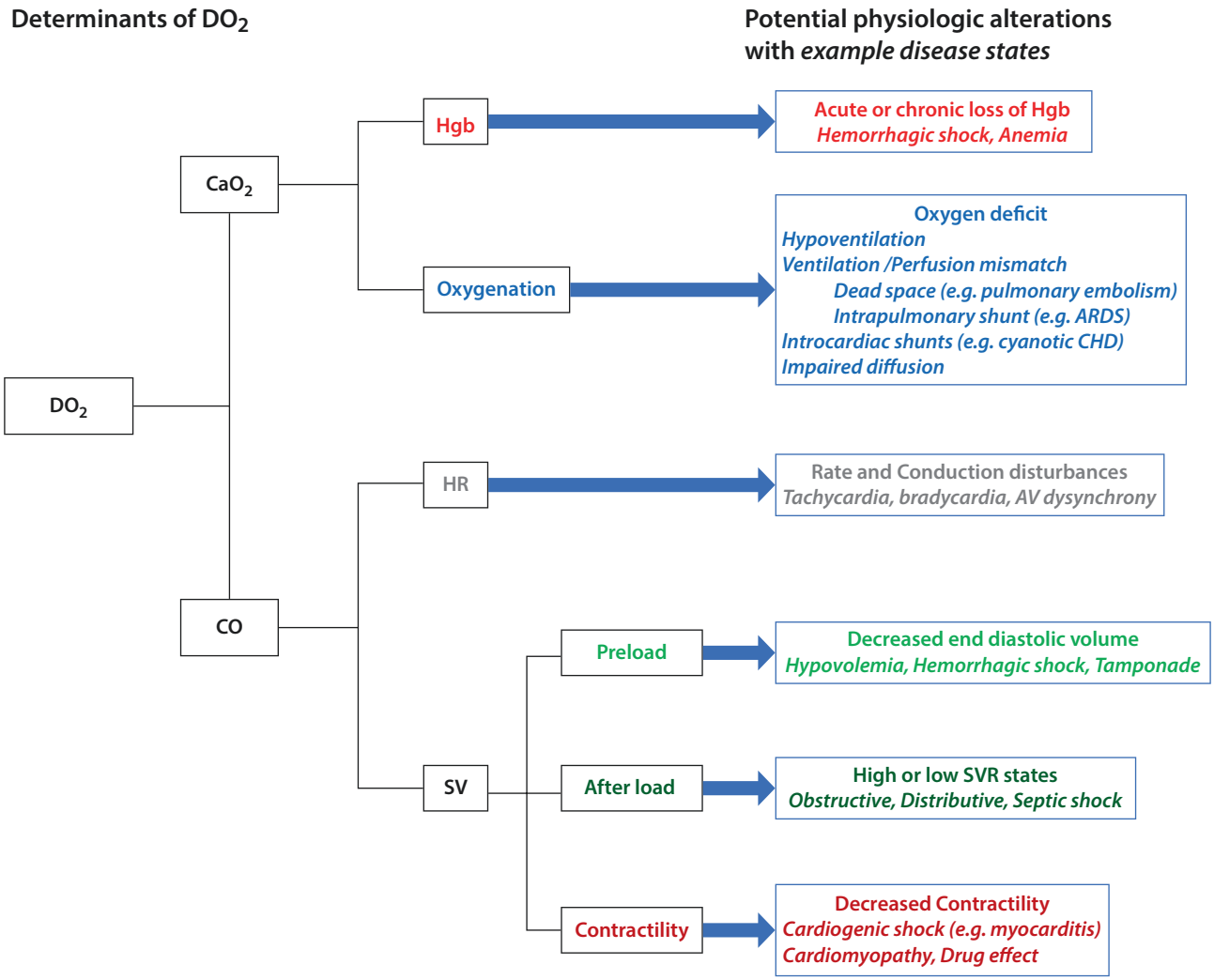


Fig. 2.3 Determinants of oxygen delivery, physiologic alterations, and corresponding disease states. (Courtesy F. Maffei). ARDS acute respiratory distress syndrome, CHD congenital heart disease, SVR systemic vascular resistance

Hgb is the hemoglobin concentration in g/dL; 1.34 is the constant that defines the maximum oxygen-binding capacity of hemoglobin in mL O_2/gm at 100% oxyhemoglobin saturation (in other words, it is the amount of oxygen a fully saturated gram of hemoglobin can carry); SaO_2 is the percent of hemoglobin saturated with oxygen; PaO_2 is the partial pressure of oxygen in the arterial blood in mm Hg; 0.003 is the constant that defines the solubility of oxygen in the blood in mL O_2/dL/mm Hg. The units for CaO_2 are mL/dL.

The formula demonstrates that a drop in oxygen saturation, as in acute respiratory failure, or a drop in the hemoglobin, as in acute hemorrhagic anemia, will significantly decrease the arterial oxygen content and, therefore, decreases oxygen delivery. The correction of the oxyhemoglobin desaturation and/or the transfusion of packed red blood cells will both increase oxygen delivery.

For example, a healthy child may have an arterial oxygen content of approximately 16.4 mL/dL (assuming a hemoglobin concentration of 12 gm/dL, 100% oxyhemoglobin saturation and a PaO_2 of 105 mm Hg).

Mathematically,

$$CaO_2 = \left[(12\,\text{g/dL}) \times (1.34\,\text{mL/g}) \times (1.00) + \begin{pmatrix} 105\,\text{mm}\,Hg \times \\ 0.003\,\text{mL/dL/mm}\,Hg \end{pmatrix} \right]$$
$$= 16.1\,\text{mL/dL} + 0.3\,\text{mL/dL} = 16.4\,\text{mL/dL}$$

In contrast, a child with hypoxia due to acute respiratory distress syndrome, (SaO_2 = 88%, PaO_2 = 60), and concomitant anemia (Hgb 9 g/dL), will have an arterial oxygen content of approximately 10.8 mL/dL.

Mathematically,

$$CaO_2 = \left[(9\,\text{g/dL}) \times (1.34\,\text{mL/g}) \times (0.88) + \begin{pmatrix} 60\,\text{mm}\,Hg \times \\ 0.003\,\text{mL/dL/mm}\,Hg \end{pmatrix} \right]$$
$$= 10.6\,\text{mL/dL} + 0.2\,\text{mL/dL} = 10.8\,\text{mL/dL}$$

Transfusing the child with packed red cells to a hemoglobin of 12 g/dL would increase his CaO_2 to 14.3 mL/dL and thereby increase his arterial oxygen content by approximately one-third.

$$(14.3 - 10.8)/10.8 = (3.5/10.8) = 0.32$$

In a child with mild anemia (hemoglobin of 9 g/dL) who has a 100% oxyhemoglobin saturation and a PaO_2 of 105 mm Hg, the arterial oxygen content would be 12.4 mL/dL.

Mathematically,

$$CaO_2 = \left[(9\,\text{g/dL}) \times (1.34\,\text{mL/g}) \times (1.0) + \begin{pmatrix} 105\,\text{mm}\,Hg \times \\ 0.003\,\text{mL/dL/mm}\,Hg \end{pmatrix} \right]$$
$$= 12.1\,\text{mL/dL} + 0.3\,\text{mL/dL} = 12.4\,\text{mL/dL}$$

An increase in the PaO_2 up to 500 mm Hg with supplemental oxygen would increase the arterial oxygen content to only 13.6 mL/dL. This would increase his CaO_2 by less than 10% [(13.6–12.4)/12.4 = (1.2/12.4) = 0.097]. Therefore, since hemoglobin cannot be more than 100% saturated, increasing the PaO_2 to high levels has minimal impact on CaO_2 except for patients suffering from severe anemia, where the dissolved oxygen represents a significant component of the total CaO_2.

This is illustrated in a child with severe anemia presenting with a hemoglobin of 5 g/dL, an oxygen-hemoglobin saturation of 100%, and a PaO_2 of 105 mm Hg. This child will have a CaO_2 of 7.0 mL/dL without supplemental oxygen.

Mathematically,

$$CaO_2 = \left[(5\,\text{g/dL}) \times (1.34\,\text{mL/g}) \times (1.00) + \begin{pmatrix} 105\,\text{mm}\,Hg \times \\ 0.003\,\text{mL/dL/mm}\,Hg \end{pmatrix} \right]$$
$$= 6.7\,\text{mL/dL} + 0.3\,\text{mL/dL} = 7.0\,\text{mL/dL}$$

Placing the child on a 100% non-rebreather mask and increasing his PaO_2 to 500 mm Hg would increase his CaO_2 to 8.2 mL/dL.

Mathematically,

$$CaO_2 = \left[(5\,\text{g/dL}) \times (1.34\,\text{mL/g}) \times (1.00) + \begin{pmatrix} 500\,\text{mm}\,Hg \times \\ 0.003\,\text{mL/dL/mm}\,Hg \end{pmatrix} \right]$$
$$= 6.7\,\text{mL/dL} + 1.5\,\text{mL/dL} = 8.2\,\text{mL/dL}$$

The increase would represent a 17% increase in his CaO_2 [(8.2 − 7.0)/7.0] = (1.2/7.0) = 0.17.

If, in addition, a transfusion was administered to increase the hemoglobin to only 8 g/dL, CaO_2 would rise significantly.

Mathematically,

$$CaO_2 = \left[(8\,\text{g/dL}) \times (1.34\,\text{mL/g}) \times (1.00) + \begin{pmatrix} 500\,\text{mm}\,Hg \times \\ 0.003\,\text{mL/dL/mm}\,Hg \end{pmatrix}\right]$$
$$= 10.7\,\text{mL/dL} + 1.5\,\text{mL/dL} = 12.2\,\text{mL/dL}$$

CaO_2 would increase an additional 50% [(12.2 − 8.2)/8.2] = (4.0/8.2) = 0.49.

Increasing dissolved oxygen content in patients with severe anemia can substantially improve oxygen delivery.

The decision regarding blood transfusions to improve oxygen delivery should not solely be based on hemoglobin concentration, except in the case of acute severe anemia. Although, mathematically, CaO_2 will increase with a PRBC transfusion, studies have revealed that a "liberal" policy of blood transfusions may be associated with increased mortality in certain critically ill patients. In a landmark study, stable, critically ill children randomized to a hemoglobin threshold of 7 gm/dL had outcomes similar to children randomized to a hemoglobin threshold level of 9.5 gm/dL. In post hoc analyses, similar results were found among the subsets of general postoperative and postoperative cardiac patients. In fact, among the subset of general postoperative patients, the restrictive transfusion strategy was associated with a shorter length of PICU stay. Several factors have been invoked to explain the lack of benefit to "liberal" transfusions, including the relative impairment of oxygen dissociation from stored blood, transfusion reactions, microcirculatory changes, volume overload, and activation of inflammatory mediators present in the transfused blood.

2.3.1.1 Arteriovenous Oxygen Content Difference

$$\text{avDO}_2 = CaO_2 - CvO_2$$

The arteriovenous difference ($CaO_2 - CvO_2$) can be used as a measure of the adequacy of O_2 delivery. With a normal O_2 consumption of approximately 250 mL/min and cardiac output of 5000 mL/min, the normal arteriovenous difference is approximately 4–6 mL O_2/dL of blood or 40–60 ml O_2/L of blood. A decrease in DO_2 leads to higher oxygen extraction, which increases the AV difference. A decrease in O_2 extraction (e.g., cyanide poisoning, sepsis) leads to a lower AV difference.

2.3.2 Cardiac Output

The second component of the oxygen delivery is systemic cardiac output (CO), the amount of blood that is being pumped to the systemic circulation in liters per minute. In the absence of intracardiac or large systemic to pulmonary shunts, the systemic cardiac output is the product of the heart rate (HR) in beats per minute and the left ventricular stroke volume (SV) in milliliters:

$$\text{CO} = \text{HR} \times \text{SV}$$

and is frequently indexed (CI) to body surface area (BSA) (m^2).

$$\text{CI} = \text{CO} / \text{BSA}$$

2

Newborns and children with noncompliant ventricles have relatively rigid ventricular walls limiting their distention. Consequently, they may have a less ability to increase stroke volume depending more on heart rate to increase cardiac output.

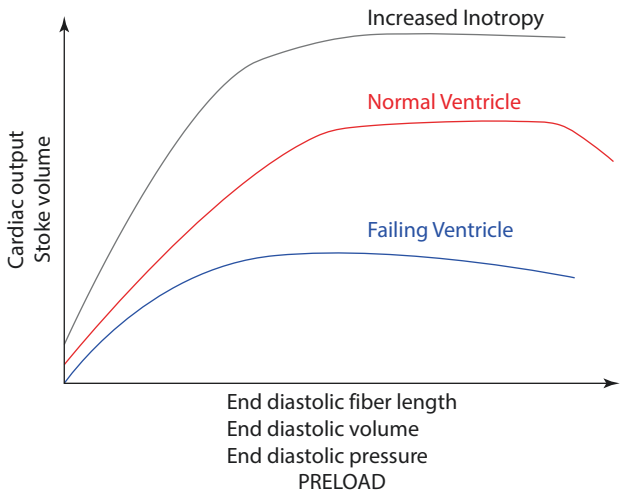
2.3.2.1 Heart Rate

The normal heart rate varies with age. Newborns and children with heart disease have relatively noncompliant ventricular walls that limit distensibility. Consequently, they have a less ability to increase stroke volume and, thus, may be more dependent on heart rate to increase cardiac output. Lack of chronotropic response limits the ability to increase stroke volume, but extreme tachycardia also limits stroke volume. Pathologically high heart rates (e.g., supraventricular tachycardia) may adversely affect cardiac output by limiting ventricular filling time during diastole, thus reducing preload and decreasing the stroke volume.

2.3.2.2 Stroke Volume

Stroke volume is the volume of blood pumped with each cardiac contraction and reflects three components: preload, contractility, and afterload. Preload is defined as the stretch of the cardiac myocytes just prior to contraction. Preload is related to the sarcomere length and is difficult to assess clinically. According to the classic Frank-Starling relationship, the strength of the muscular contraction depends on the initial length (stretch) of the muscle. As the stretch of the cardiac myocyte is increased, the strength of the muscular contraction increases up to a point. The cardiac myocyte can be stretched to a point beyond which maximal contraction occurs, and the strength of the contraction begins to decrease as further stretching of the myocyte occurs (◘ Fig. 2.4). Clinically determining preload can be difficult. The left ventricular end-diastolic volume, which is the volume of blood in the left ventricle just prior to contraction, is probably the best surrogate of systemic preload.

Thermodilution techniques are available that can determine global end-diastolic volume but are invasive and not well established in pediatric critical care. Echocardiography and magnetic resonance imaging may also be used to estimate left ventricular end-diastolic volume but are technician dependent and do not allow for moment-to-moment monitoring.



◘ **Fig. 2.4** Frank-Starling relationship between preload and ventricular function. The *middle curve* represents a normal myocardium. As preload increases, markers of contractility increase. *The lower curve* represents a myocardium that is dysfunctional. The curve is shifted downward and to the right, such that for the same preload, there is decreased ventricular function. Finally, *the upper curve* represents the normal myocardium receiving inotropic support. Note that the curve is shifted upward and to the left, such that for the same preload, there is increased ventricular function

Left ventricular end-diastolic volume may be estimated by left ventricular end-diastolic pressure. This estimation may be confounded by a change in the distensibility of the ventricular wall or pressure increases outside of the ventricle (increased intrathoracic pressure, pericardial tamponade, etc.).

Left atrial pressure has been used as an indirect measure of preload but requires the placement of a pulmonary artery catheter (PAC). Using the PAC, the pulmonary artery occlusion pressure can be obtained and will reflect left atrial pressure, which can be a clinically useful surrogate of systemic preload. The pulmonary artery occlusion pressure is determined by inflating the balloon of a pulmonary artery catheter such that it floats out and wedges into a distal pulmonary artery. The distal lumen of the pulmonary artery catheter is distal to the balloon and, therefore, measures the downstream pressure without interference from proximal pressures as the inflated balloon isolates the distal pressures. Placement of a PAC is invasive, and adult studies have suggested that the routine use of such monitoring may be associated with worse outcomes.

Central venous pressure, as measured in the right atrium or a major vein within the thoracic compartment, has been used to estimate preload. The ability of central venous pressure to reflect true preload may be impeded by multiple factors, including ventricular compliance and atrioventricular valvular disease. However, because of its clinical availability, it is commonly used to assist in the assessment of preload.

In addition to preload, stroke volume is determined by contractility. Cardiac contractility is defined as the extent of shortening that occurs in cardiac myocytes when stimulated independent of preload or afterload. It refers to the intrinsic strength of the myocardial muscle and is the measure of cardiac muscle performance. It depends on many factors, including the mass of muscle, the molecular aspects of muscular contraction, the degree of stimulation by catecholamines, and the concentration of electrolytes, such as calcium, potassium, and magnesium. Factors that increase cardiac contractility move the Frank-Starling curve upward and to the left (◘ Fig. 2.4). Thus, for the same preload, increased contractility usually results in increased stroke volume.

Like preload, clinically determining contractility is difficult. Techniques such as the thermodilution-derived cardiac function index and the echocardiographic stress index have been developed, but their application to pediatrics has been limited to date. Doppler tissue imaging represents a new echocardiographic technique that may assist in the determination of contractility by measuring the velocity of myocardial motion. Echocardiographic determination of the shortening fraction and the ejection fraction remain the most commonly utilized surrogates of contractility.

The shortening fraction (at times referred to fractional shortening) is the percent change in the diameter of the left ventricle, which occurs with contraction. It is determined by taking the difference in left ventricular diameter between diastole and systole and dividing that value by the left ventricular end-diastolic diameter. Normal values for shortening fraction in infants and children are between 28% and 46%. The shortening fraction assumes that the ventricle has a symmetric cylindrical shape and has a normal volume state. Diseases with abnormally shaped ventricles (e.g., hypoplastic left ventricle) and those causing asymmetric wall abnormalities reduce the ability of shortening fraction to reflect the overall systolic function.

Contractility depends on many factors, including the mass of muscle, the molecular aspects of muscular contraction, the degree of stimulation by catecholamines, and the concentration of electrolytes, such as calcium, potassium, and magnesium. Factors that increase cardiac contractility move the Frank-Starling curve upward and to the left.

The ejection fraction is another echocardiographic parameter that can be used to asses left ventricular function. It is determined in a manner like the shortening fraction, but it utilizes end-diastolic volumes rather than diameters. Normal values tend to range from 55% to 65%. Ejection fraction is categorized as normal (≥55%), slightly reduced (41–55%), moderately reduced (31–40%), and markedly reduced (≤30%).

Afterload may be defined as the force opposing contraction of the left ventricular myocytes during systole. It can be quantified as the left ventricular wall stress. The left ventricular wall stress may be estimated using the Law of Laplace, which relates wall stress to the pressure, radius, and thickness of a sphere or cylinder in the following formula:

$$\text{Wall stress} = (\text{Pressure})(\text{Radius}) / (\text{Wall thickness})$$

Because the left ventricle is not a sphere or cylinder, the application of the Law of Laplace is an oversimplification. In using this equation to assess left ventricular afterload, the pressure refers to the transmural left ventricular pressure, the radius refers to the left ventricular end-systolic dimension, and the wall thickness to the left ventricle wall. These measures should all be taken at the end of left ventricular systole. The left ventricular wall thickness and dimension may be determined echocardiographically. The transmural left ventricular pressure is the difference between the pressure inside the ventricle and the pressure outside the ventricle.

The determinants of the cardiac output (heart rate, preload, afterload, and contractility) and the arterial content of oxygen (hemoglobin and oxygenation) can each become deranged in critically ill patients. Careful monitoring and adjustment of these variables are required in order to achieve the best clinical outcome.

Extraventricular pressures have been determined using esophageal or pleural pressure monitoring, although clinically these values are not commonly measured. It is important to note that the use of positive-pressure ventilation will change the intrathoracic pressure from a negative to a positive. As such, positive-pressure ventilation will decrease left ventricular afterload because subtracting a positive from a positive (the intraventricular pressure) is a smaller number. In contrast, normal, negative-pressure ventilation results in increased left ventricular afterload because subtracting a negative (intrathoracic pressure) from a positive (intraventricular pressure) results in a higher number (i.e., increased afterload).

2.4 Interdependence of the Heart, Lungs, and Blood on Peripheral Oxygen Delivery

Oxygen delivery is dependent upon multiple variables, all of them intimately related. Any derangements of the determinants of **arterial oxygen content** (hemoglobin concentration, oxygenation) or **cardiac output** (preload, contractility, afterload, or heart rate) will affect oxygen delivery.

The lungs have the primary role of extracting oxygen from inspired gas. The blood has the primary role of carrying that oxygen to the tissues, and the heart has the primary responsibility of circulating that blood and oxygen to the tissues. These three systems work interdependently to assure adequate oxygen delivery to the tissues. This interdependence is best exemplified by reviewing the physiologic responses to alterations in any of these systems.

One of the most common causes of inadequate oxygen delivery in pediatrics is acute hypoxemia. Hypoxemia is detected in vivo by chemoreceptors located in the carotid and aortic bodies. When these chemoreceptors are triggered by hypoxemia (PaO_2 < 60 mm Hg, corresponding to SaO_2 < 93%), there is stimulation of the respiratory area of the medulla. This results in an increase in minute ventilation, a higher alveolar oxygen concentration (PAO_2), and ultimately, an increase in the arterial oxygen content as a result of the increase in the oxygen saturation and the PaO_2. Furthermore, signals are sent from the chemoreceptors to the vasomotor center of the brainstem, leading to increased sympathetic tone. This sympathetic stimulation increases the heart rate, improves the preload by venous constriction, and increases contractility, all of which improve cardiac output and, thereby, augment oxygen delivery.

Sympathetic-mediated compensatory responses have the potential to become maladaptive, resulting in increased afterload and increased oxygen consumption by the myocardium. When prolonged, this compensatory response may lead to myocardial dysfunction, especially in the setting of preexisting cardiac disease. These compensatory mechanisms are not well developed in newborns who often develop hypotension, bradycardia, and apnea in response to acute hypoxemia.

Hypoxemia is detected by special nerve chemical receptors located in the carotid and aortic bodies. When these chemoreceptors are triggered by hypoxemia (PaO_2 < 60 mm Hg, corresponding to SaO_2 < 93%), there is stimulation of the respiratory area of the medulla. This results in an increase in minute ventilation, a higher alveolar oxygen concentration (PAO_2), and, ultimately, an increase in the arterial oxygen content as a result of the increase in the oxygen saturation and the PaO_2.

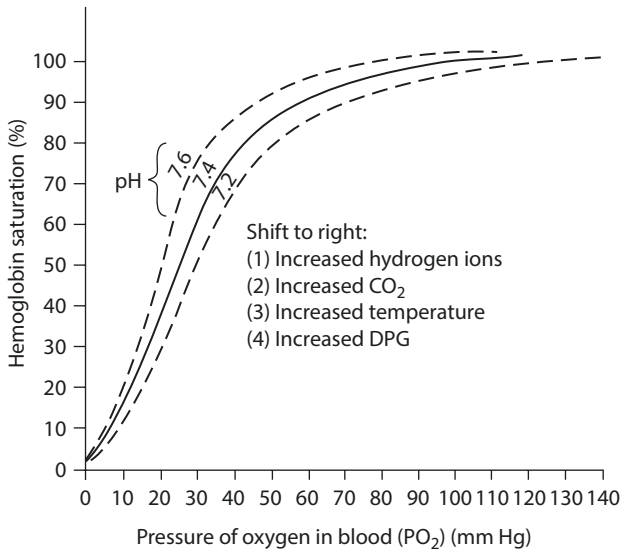
Hemoglobin is the molecule responsible for carrying oxygen in the blood. It can adapt to physiologic changes associated with hypoxia to improve oxygen delivery to the tissues. In the presence of acidosis, which often accompanies hypoxia, hemoglobin's affinity for oxygen decreases, facilitating the release of oxygen to the starved cells (■ Fig. 2.5). The affinity of hemoglobin for oxygen is also decreased in the presence of increased concentrations of 2,3 diphosphoglycerate (2,3 DPG), which occur in the presence of hypoxemia.

Of note, the concentration of 2,3 DPG declines over time in stored packed red blood cells. This loss of 2,3 DPG decreases the ability of PRBC transfusion to release oxygen at the tissue level. In addition, it is important to recognize that there are different forms of hemoglobin with different affinities for oxygen. For example, fetal hemoglobin constitutes a significant proportion of the total hemoglobin in newborns and small infants. This form of hemoglobin has an increased affinity for oxygen, which facilitates the transfer of oxygen from the maternal adult hemoglobin across the placenta. However, following birth, when the oxygen concentration at the pulmonary alveolar level is much higher, this increased affinity for oxygen is no longer needed. In fact, this elevated affinity for oxygen may impair the unloading of oxygen at the tissue level postnatally, which may be problematic in conditions associated with decreased oxygen delivery.

Certain factors may decrease oxyhemoglobin dissociation in the capillary circulation, thereby making less oxygen available. Factors that shift the oxygen-hemoglobin dissociation curve to the left include severe alkalosis, the depletion

Factors that shift the oxyhemoglobin dissociation curve to the **r**ight promote the **r**elease of oxygen from Hgb, whereas factors that shift the curve to the **l**eft promote **l**atching of oxygen onto Hgb.

In the presence of acidosis, the affinity of hemoglobin for oxygen decreases, facilitating the release of oxygen to the starved cells. The affinity of hemoglobin for oxygen also decreases with increases in the concentration of 2,3 diphosphoglycerate (2,3 DPG), which occur in the presence of hypoxemia.



■ **Fig. 2.5** The oxyhemoglobin dissociation curve. The curve is shifted to the right by factors that enhance oxyhemoglobin dissociation and allow oxygen to be more readily available to the tissues. These factors include 2,3-diphosphoglycerate (2,3 DPG), which may be increased by glycolysis, exercise, hypoxemia, fever, and/or acidosis. The curve is shifted to the left by severe alkalosis, the depletion of 2,3 DPG, the presence of fetal hemoglobin, and certain hemoglobinopathies

of 2,3-diphosphoglycerate (2,3 DPG), fetal hemoglobin, and certain hemoglobinopathies. Factors that shift the oxygen-hemoglobin dissociation curve to the right and promote the release of oxygen to the tissues and include increased 2,3 DPG, exercise, hypoxemia, fever, and/or acidosis.

Tissue hypoxia triggers the kidney to secrete the hormone erythropoietin, stimulating the bone marrow to increase the production of red blood cells.

Sustained hypoxia induces changes in cellular gene expression. A family of transcription factors, known as hypoxia-inducible factors (HIF), has been characterized, furthering the understanding of the molecular response to hypoxia. When oxygen saturation is chronically low, as in cyanotic heart disease, the bone marrow responds by increasing the red blood cell production, leading to an increased hemoglobin concentration and improved CaO_2. The molecular signal in this response is the hormone erythropoietin secreted by the kidney. Erythropoietin stimulates the bone marrow to increase the production of red blood cells. When hypoxemia is chronic and severe (e.g., uncorrected cyanotic heart disease), the resultant polycythemia increases blood viscosity and the resistance to blood flow in the microcirculation. This may result in compromised oxygen delivery to tissues despite a high hemoglobin concentration.

When hemorrhagic shock is the cause of inadequate oxygen delivery, baroreceptors located in the carotid sinus, aortic arch, and venoarterial junctions of both atria are triggered. Triggering of these baroreceptors stimulates the brainstem to increase the cardiac output primarily through an increase in the heart rate, to compensate for the low arterial oxygen content. When hypovolemia compromises cardiac output, peripheral vasoconstriction results, optimizing perfusion of vital organs and minimizing the risk of ongoing bleeding.

Multiple compensatory responses exist to preserve DO_2 during low cardiac output states. Low cardiac output may be secondary to hypovolemia, cardiogenic shock, or distributive shock. Reponses include increasing systemic vascular resistance, conserving salt and water, and increasing heart rate and contractility.

If physiological alterations occur gradually, adequate compensation is more likely to occur. This is especially true regarding the development of anemia. Chronic anemia, as occurs with iron deficiency, allows for maintenance of oxygen delivery by gradual increases in preload and heart rate and, therefore, cardiac output. Additional capillary beds open within vital organs minimizing the distance from the oxygen supply to the cells. These opened capillary beds result in a decreased systemic vascular resistance, which fosters an increased cardiac output and manifests itself as a widened pulse pressure with decreased diastolic pressures. Unlike acute anemia, intravascular volume is not only maintained but may be elevated. Even children with a hemoglobin concentration less than 4 g/dL can compensate remarkably well if the anemia has developed slowly. However, it is important to recognize that compensation results in a hypervolemic, high cardiac output state. Traditionally, very small aliquots of red blood cells transfused over 3–4 h were used in the correction of long-standing severe anemia. Transfusion volumes of 4–8 mL/kg may be tolerated because the overall improvement in oxygen delivery outweighs the potential for volume overload, particularly when diuretics are used concomitantly.

During low cardiac output states, baroreceptors throughout the body sense the inadequate flow and the compensatory mechanisms begin (▶ Box 2.1). Sympathetic activation results in catecholamine secretion and peripheral vasoconstriction. This leads to shunting of blood from the periphery to the core circulation to optimize oxygen delivery to the brain and heart. The heart rate increases in response to the release of catecholamines. The increase in chronotropy attempts to preserve cardiac output if stroke volume is decreased.

To increase preload, renin-angiotensin-aldosterone and antidiuretic hormone are secreted, resulting in salt and water retention. The respiratory rate increases, thereby lowering the CO_2, improving alveolar oxygen, and, ultimately, increasing the arterial oxygen content. With disease progression, these compensatory mechanisms may produce physiologic impairment and ultimately may become overwhelmed.

Box 2.1 Compensatory Responses to Poor Cardiac Output That Act to Preserve DO_2

Baroreceptors sensing a fall in CO initiate complex and interconnected cascade to maintain blood pressure and cerebral and coronary perfusion. Key elements of the response include:

- Sympathetic activation results in catecholamine secretion.
- Neuroendocrine chemo- and osmoreceptor response increase stress hormone secretion (e.g., catecholamines, cortisol, antidiuretic hormone).
- Reduced renal blood flow activates the renin-angiotensin system, resulting in angiotensin II-mediated vasoconstriction.
- Decreased capillary hydrostatic pressure promotes movement of interstitial fluid to the vascular space.

The result is preservation of systolic blood pressure at the expense of shunting blood from splanchnic organs, the kidney and skin. The examination findings that reflect these compensatory mechanisms include cool skin, delayed capillary refill, and narrowed pulse pressure (i.e., systolic pressure preserved, diastolic increased).

2.5 Oxygen Consumption

Oxygen consumption (VO_2) is the amount of oxygen consumed by the tissues per minute and is related to energy expenditure. Energy expenditure is the amount of energy consumed from substrates (carbohydrates, lipids, amino acids) during the process of energy generation. Energy expenditure can be measured and/or estimated from the oxygen consumption and carbon dioxide production.

Energy expenditure can be measured directly with calorimetric methods or can be estimated from oxygen consumption, using specific formulas to convert it to energy.

Critically ill children may have abnormally high or low oxygen consumption (Table 2.1). Oxygen consumption may be low because the metabolic activity of the tissues has decreased (e.g., barbiturate-induced coma, hypothermia) and the tissues have impaired oxygen uptake (e.g., cyanide toxicity) or because of inadequate supply.

When oxygen consumption is low because of inadequate supply, the cause may be the result of a derangement of one of the determinants of oxygen delivery. Cellular hypoxia may occur in the setting of mismatched oxygen consumption (high) and oxygen delivery (low). In some circumstances, the abso-

Table 2.1 Factors affecting VO_2

Factors that increase VO_2	Factors that decrease VO_2
Inflammation	Inadequate DO_2
Hyperpyrexia	Impaired cellular uptake
Shivering	Hypothermia
Pain	Mechanical ventilation
Agitation	Sedation/analgesia/NMB
Increased work of breathing	Coma, brain death

lute value of oxygen consumption may be high when compared to normal values, but the tissues may still be starving because oxygen demands are higher yet. Most tissues can increase their extraction of oxygen severalfold to satisfy their oxygen needs.

Under normal conditions, oxygen delivery is determined by the oxygen needs of the tissues. If the cells do not need additional oxygen, increasing oxygen delivery will only minimally impact oxygen consumption (supply independent). However, if the tissues are starving for oxygen despite increasing the amount of oxygen extracted from the blood, consumption will begin to fall linearly with decreasing oxygen delivery. The point at which this occurs is termed the critical point of oxygen delivery. Below that point, cells are resorting to anaerobic metabolic pathways to survive. This is termed the supply-dependent portion of the oxygen consumption curve (Fig. 2.6).

In critically ill patients with sepsis or acute respiratory distress syndrome (ARDS), this normal biphasic relationship may not occur. Oxygen consumption may continue to increase, even as DO_2 increases beyond values seen in healthy individuals. Oxygen consumption remains supply dependent to much higher levels of oxygen delivery. This leads to "pathologic supply dependency" (Fig. 2.7). The reason for this alteration in the normal relationship between oxygen supply and delivery has not been clearly elucidated and seems to apply primarily to sepsis and ARDS. It has been suggested that it occurs because the critical point of oxygen delivery has been reset to a much higher point. Alternatively, it may be the result of impaired ability of the tissues to increase oxygen extraction.

2.5.1 Measurement Techniques

The determination of oxygen consumption provides insight into the adequacy of oxygen delivery and utilization at the tissue level. However, accurately determining oxygen consumption at the tissue level is extremely difficult. Several methods for the determination of oxygen consumption have been developed for clinical use. One approach is to assess the composition of inhaled and exhaled respiratory gases and determine oxygen consumption using indirect calorimetry.

Indirect calorimetry is based on the basic law of thermodynamics that energy utilization entails the consumption of oxygen with the production of carbon dioxide, nitrogenous waste, and water in a stoichiometric fashion.

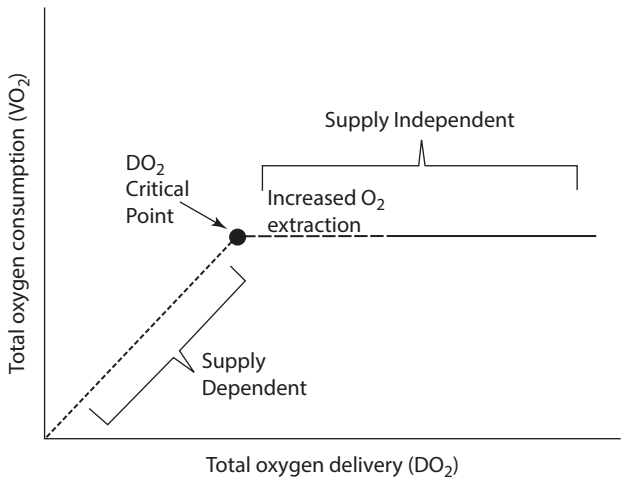


Fig. 2.6 Oxygen consumption/oxygen delivery relationship

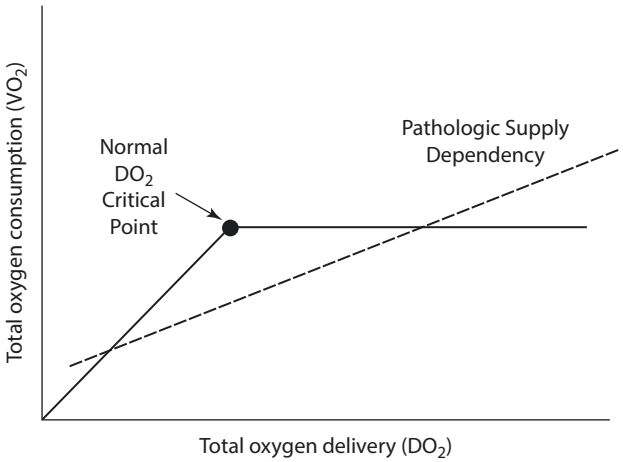


Fig. 2.7 The oxygen consumption/oxygen delivery relationship in pathologic states such ARDS and sepsis. In this figure, the *solid line* represents the normal biphasic relationship between oxygen consumption and delivery. The *dotted line* represents the pathologic relationship observed in critically ill patients with sepsis or ARDS. In this condition, supply dependency is observed at much higher levels of oxygen delivery. (Adapted from Crocetti and Krachman (2002))

Commercially available indirect calorimetry machines require that the patient breathes through a valved system that separates inspired and expired gases. The inspired gas has a known concentration of oxygen, nitrogen, and carbon dioxide. The volume of expired gas is measured, and the amount of expired oxygen and carbon dioxide is determined. With these values, oxygen consumption (VO_2) can be determined using the following equation:

$$\dot{V}O_2 = \dot{V}_I\left(F_IO_2\right) - \dot{V}_E\left(F_EO_2\right) \quad \left(\dot{V}CO_2\right) = \dot{V}_E\left(F_ECO_2\right) - \dot{V}_I\left(F_ICO_2\right)$$

where VO_2 is the oxygen consumption, V_I is the volume of inspired gas, F_IO_2 is the fraction of oxygen in the inspired gas, V_E is the volume of exhaled gas, F_EO_2 is the fraction of oxygen in the exhaled gas, VCO_2 is the production of carbon dioxide, F_ICO_2 is the fraction of carbon dioxide in the inspired gas, V_E is the volume of exhaled gas, and F_ECO_2 is the fraction of carbon dioxide in the exhaled gas. This approach can be fraught with error particularly if there are leaks in the respiratory circuit (including around the endotracheal tube) and if the F_IO_2 is greater than 0.40. Consequently, other methods to estimate oxygen consumption have been developed.

The reversed Fick equation uses the arteriovenous oxygen saturation difference to estimate oxygen consumption. It requires determination of the cardiac output, the arterial oxygen content, and the mixed venous oxygen content. The measurement of cardiac output and mixed venous oxygen content requires the placement of a pulmonary artery catheter.

The reversed Fick equation uses the arteriovenous oxygen content difference to estimate oxygen consumption. It requires determination of the cardiac output, the arterial oxygen content and the mixed venous oxygen content. Using this method, oxygen consumption will be equivalent to the difference between the arterial and mixed venous oxygen content, multiplied by the cardiac output.

$$\dot{V}O_2 = \left(CaO_2 - CmvO_2\right) \times CO$$

Oxygen consumption is measured in units of mLs of oxygen consumed per minute. As such, the above equation is multiplied by a factor of 10 to account for units.

$$\dot{V}O_2\left(mL/min\right) = \left(CaO_2\left(mL/dL\right) - CmvO_2\left(mL/dL\right)\right) \times CO\left(L/min\right) \times 10\left(dL/L\right)$$

Like the measurement of intracardiac pressures, the determination of cardiac output and mixed venous oxygen content requires the placement of a PAC. Placement of a PAC can be technically difficult in small infants. In addition, PAC-derived data has multiple limitations which has led to its decrease use in pediatric critical care.

2.5.1.1 Mixed Venous and Central Venous Oxygen Saturation

At rest, the body normally extracts only 25% of the total amount of oxygen delivered. Provided that cardiac output is adequate to meet tissue oxygen demand and the hemoglobin concentration is in the normal range, ~25% of the delivered oxygen is consumed. Therefore, in a healthy steady state, DO_2 is luxurious when compared to oxygen demand with approximately 75% of the oxygen delivered remaining unused. Of note, oxygen extraction varies across organ beds with some organs being high extractors (e.g., the brain and myocardium) and other organs being low extractors (e.g., skin and kidneys).

A true mixed venous saturation ($SmvO_2$) requires the placement of a PAC to sample pulmonary artery blood. Without a pulmonary artery catheter in place, the pulmonary artery $SmvO_2$ can be approximated by sampling venous blood from a central catheter with its tip located at the SVC-RA junction. Venous blood oxygen saturation from the SVC-RA junction is referred to as a central venous oxygen saturation ($ScvO_2$) or right atrial saturation. The $ScvO_2$ can be an estimate of the adequacy of global oxygen delivery. If the oxygen delivery is insufficient to meet cellular oxygen demands, oxygen extraction by the starved tissues will increase, and $ScvO_2$ will decrease.

The $ScvO_2$ can be an estimate of the adequacy of global DO_2. If DO_2 is insufficient to meet cellular oxygen demands, oxygen extraction will increase, and $ScvO_2$ will decrease.

Adequate oxygen delivery results in normal oxygen extraction and a normal $ScvO_2$ of greater than 70%. The use of $ScvO_2$ has grown as an endpoint of resuscitation in adult and pediatric critical care. The same principle can be applied to assess oxygen delivery and consumption in regional beds, such as the cerebral circulation, by measuring the venous oxygen saturation in the jugular vein.

Like indirect calorimetry, the reversed Fick procedure has several limitations that must be taken into consideration when interpreting its results. For example, it provides an estimation only of global oxygen consumption; important regional differences may not be detected by this method (Table 2.2). In addition, oxygen extraction may be blocked by metabolic toxic factors. In this setting, the oxygen extraction would be normal or decreased, resulting in a

Table 2.2 Organ-specific distribution of blood flow, percent cardiac output and $avDO_2$, oxygen extraction ratio

Organ	Resting blood flow (mL/100 g/min)	Maximal blood flow (mL/100 g/min)	Potential flow increase (fold)	Percentage of resting cardiac output	$avDO_2$ mL of O_2 per 100 mL blood (O_2ER)
Brain	54	140	2.6	14	6 (31%)
Heart	70	390	5.6	4.5	11 (57%)
Liver/splanchnic	98	250	2.6	25	5 (26%)
Kidney	310	390	1.25	20	1.5 (7.8%)
Muscle	4	18	4.5	21	5 (26%)
Skin	8	150	19	7.5	2 (10%)

high central or mixed venous saturation despite the presence of tissue oxygen starvation. Although cyanide poisoning is the classic example of impaired oxygen utilization, experimental studies suggest that endotoxin may block oxygen metabolism under certain circumstances (e.g., septic shock).

The presence of an intracardiac, left-to-right shunt will complicate interpretation of the Fick equation as the pulmonary artery saturations will be "contaminated" with the highly saturated blood returning from the lungs to the left side of the heart. Depending on the degree of the shunt, the oxygen saturations will be higher than that of the central venous system. Finally, a traditional critique of the Fick equation was that it provided an estimate of oxygen consumption at isolated points in time. Given that the physiology of the critically ill child may change rapidly, clinically significant changes may not be detected.

With the advent of oximetric catheter technology, the central venous oxygen saturation can be measured continuously. It is important to note that when continuous oximetric monitoring is performed in a central vein rather than the pulmonary artery, the position of the catheter may influence the venous saturation. For example, a central venous catheter placed in the inferior vena cava is likely to reveal a higher oxygen saturation because the kidneys, acting primarily as filters, typically consume relatively little oxygen. In contrast, a central venous catheter placed in proximity to the coronary sinus may reveal low venous saturations as the oxygen extraction of myocardial tissue by mass is higher than other tissues.

There is a wide variability in organ resting and maximal blood flow rates. The ability to extract oxygen also varies widely among individual organs. The heart and brain are very high extractors, whereas high flow filtering organs like the kidney and liver are relatively low oxygen extractors (Table 2.2).

Central venous oxygen saturations can be measured continuously, thus overcoming limitations of the classic Fick procedure which requires PAC placement.

2.6 Oxygen Consumption Variability

2.6.1 Factors That Affect Oxygen Consumption

A multitude of factors can affect oxygen consumption (Fig. 2.8). Oxygen consumption can be increased by several pathological conditions, including catabolic states (e.g., sepsis, burns, fever). During fever, oxygen metabolism must be increased to generate the excess of energy lost as heat. In addition,

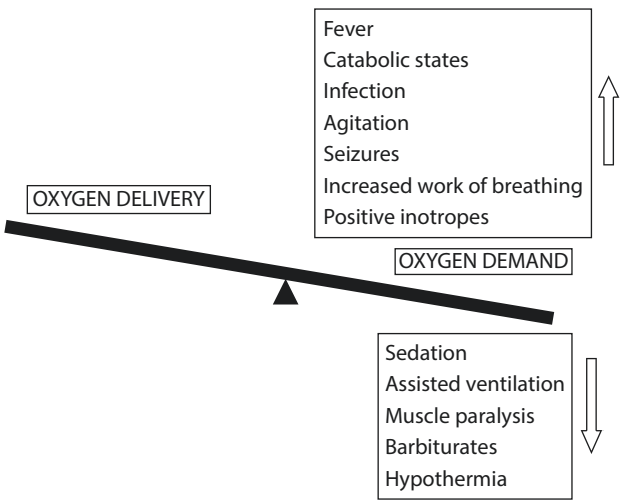


Fig. 2.8 Factors affecting oxygen utilization

oxygen consumption is increased during episodes of increased motor activity. Increased motor activity may occur with agitation, shivering, or seizures. Seizures can profoundly increase oxygen consumption.

Increased work of breathing may substantially increase the consumption of oxygen; as much as 40% of the cardiac output may be required to support excessive work of breathing. The initiation of mechanical ventilation in the setting of respiratory distress can be used to substantially decrease the consumption of oxygen. The need to decrease oxygen demand is an appropriate indication for the use mechanical ventilation in the treatment of shock.

Infusions of inotropic medications increase myocardial oxygen consumption. The increase is associated with the excess energy needed to increase the contractile force of the myocardial tissue, as well as the associated increase in heart rate caused by most catecholamines. Vasopressors may further increase myocardial oxygen consumption secondary to the additional energy needed to pump against the increased vascular resistance. Phosphodiesterase III inhibitors, such as milrinone increase the contractility without chronotropic or alpha-adrenergic effects. However, myocardial oxygen consumption will still increase in response to the additional myocardial work.

VO_2 is increased by catabolic states, fever, infection, increased motor activity, increased work of breathing, and the use of inotropic agents. VO_2 is decreased by sedation and paralysis, mechanical ventilation, barbiturate coma, hypothermia, and severe anoxic-ischemic brain injury.

In contrast, several clinical conditions and medical interventions may result in a decrease in oxygen consumption. For example, the use of sedation and neuromuscular blockade may result in decreased muscular activity, decreased agitation, and inhibition of catecholamine production, thereby decreasing the consumption of oxygen. Understanding that the brain is one of the most metabolically demanding organs, any condition that results in significantly diminished brain activity will be associated with dramatically decreased oxygen consumption. Barbiturate-induced coma to treat brain injury or status epilepticus represents one such example. Brain death is perhaps the most extreme example. Similarly, hypothermia globally decreases the metabolic demands of the body, including the brain, and, therefore, may be associated with decreased oxygen consumption. This effect of hypothermia is used clinically to reduce the oxygen needs of the body in certain settings, such as during cardiac surgery or following cardiac arrest.

2.7 Oxygen Extraction

The oxygen extraction ratio (O_2ER) is the fraction of the arterial oxygen content that is consumed as the blood traverses the organ or tissue. It is determined by dividing the difference of the arterial and venous oxygen content by the arterial oxygen content:

$$O_2ER = \left(CaO_2 - CvO_2\right) / CaO_2$$

$$O_2ER = avDO_2 / CaO_2$$

The normal oxygen extraction ratio is 0.2–0.3, indicating a significant excess capacity of oxygen being delivered under normal circumstances.

The normal global O_2ER is only 0.2–0.3, reflecting an excess of oxygen being delivered to the tissues. This excess provides an added margin should oxygen delivery becomes compromised, thereby minimizing the need for anaerobic metabolism. The oxygen extraction ratio varies widely with differences in the basal metabolic activities of different tissues (Table 2.1). Organs with higher metabolic demand will consume more oxygen. Consequently, the venous oxygen content in these tissues will be lower, and they will have higher oxygen extraction ratios.

The oxygen saturation, and hence the oxygen content, of the coronary venous blood is the lowest in the body. The myocardial oxygen extraction ratio

is very high (~0.6). During conditions of reduced supply, the myocardium has limited ability to increase the oxygen extraction. This places the myocardial tissue vulnerable to ischemia.

The brain is also characterized by high metabolic demands, thereby creating a high oxygen extraction ratio. The adequacy of oxygen delivery to the brain has been evaluated by measuring the venous saturation of the blood in the jugular bulb. Other organs such as the skin and the intestinal tract have relatively low oxygen demands. In conditions of compromised oxygen delivery, blood flow is shunted away from these tissues and reserved for the more integral organs. This process is usually well tolerated but may lead to tissue ischemia in certain circumstances. For example, the use of vasoactive infusions, such as epinephrine or norepinephrine during conditions of compromised oxygen delivery, may increase the vasoconstriction of the intestinal vessels and further decrease the oxygen delivery to these tissues. The relative ischemia of the intestinal tissue has been one of the precipitating factors for the systemic inflammatory response syndrome. According to this theory, ischemia compromises the integrity of the intestinal epithelium, allowing bacteria and bacterial products to gain access to the circulation and activate the inflammatory response. This is the rationale for the use of gastric tonometry as a surrogate for splanchnic oxygen delivery.

In addition to variations among individual organs, oxygen extraction varies with disease states. For example, in the setting of septic shock, the oxygen extraction ratio may be low, high, or normal, depending on the balance of oxygen demand, supply, and utilization. In conditions that block the utilization of oxygen, such as cyanide poisoning, the oxygen extraction ratio will appear low to normal despite the presence of cellular hypoxia.

2.8 Assessment of Oxygen Delivery/Oxygen Consumption

The clinical evaluation of the match between oxygen delivery and oxygen consumption is integral to the practice of pediatric critical care medicine.

Serial physical examinations performed by a trained clinician is the most useful tool in estimating the adequacy of oxygen delivery. This is the basic premise of the Pediatric Advanced Life Support (PALS) course established by the American Heart Association. The clinical evaluation of end-organ delivery of oxygen is initially performed by rapid physical examination, which includes the assessment of peripheral perfusion, heart rate, blood pressure, urine output, and mental status.

The clinical evaluation of the match between oxygen delivery and oxygen consumption is integral to the practice of pediatric critical care medicine. Clinical signs of poor cardiac output such as poor peripheral perfusion, tachycardia, or altered mental status must be quickly recognized to ensure prompt interventions.

Measurable components of CaO_2 (e.g., hemoglobin and the oxygen saturation) should be obtained when oxygen delivery is suspected to be inadequate. Additional laboratory studies may provide therapeutic targets. Electrolytes important in cardiac contractility and electrical propagation should be evaluated and include ionized calcium, potassium, and magnesium. Arterial blood pH should be measured as severe acidosis can negatively affect contractility. Anaerobic metabolism will lead to an elevation in the hydrogen proton concentration in the blood and will be manifested as metabolic acidosis and a rising base deficit. Elevation of blood lactate in the presence of acidosis should alert the clinician to the likelihood of tissue hypoxia.

Serial measures of acidosis *(pH, base deficit),* lactate, $SmvO_2$, or $ScvO_2$ can help the clinician identify states of declining DO_2 and high oxygen extraction. Rising lactate and falling $ScvO_2$ or $SmvO_2$ are consistent with anaerobic metabolism. Utilizing exam findings and biomarkers, pediatric critical care providers can conceptualize whether the critically ill child they are caring for is improving or deteriorating based on the DO_2-VO_2 relationship (◘ Fig. 2.9).

Serial measures of acidosis (pH, base deficit), lactate, $SmvO_2$, or $ScvO_2$ can help the clinician identify states of declining DO_2 and high oxygen extraction consistent with anaerobic metabolism.

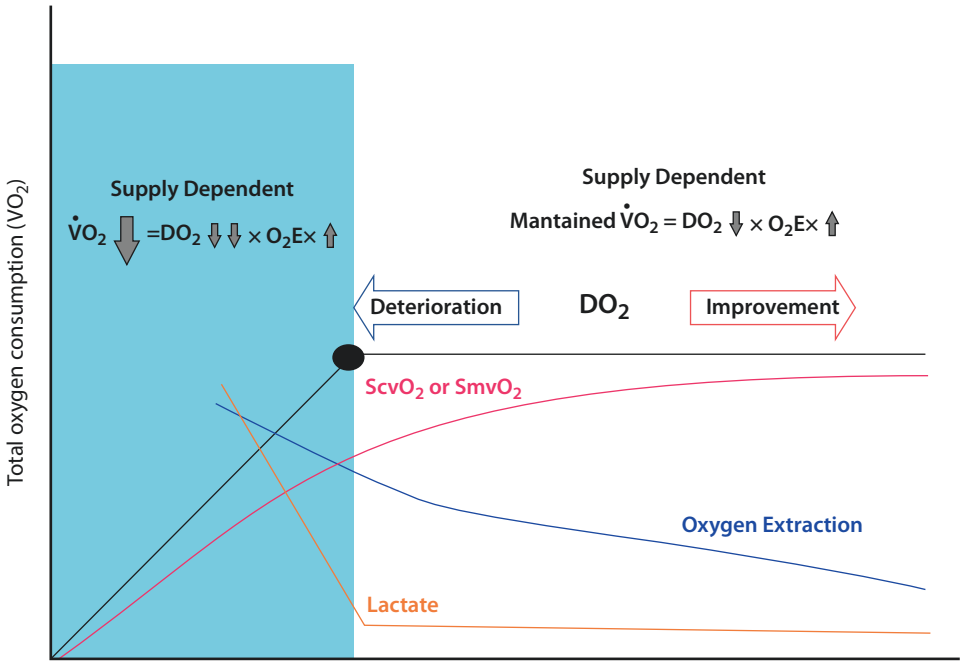


Fig. 2.9 The relationship between oxygen delivery (DO_2), oxygen consumption (VO_2), oxygen extraction (O_2Ex), and central or venous saturation ($ScvO_2$ or $SmvO_2$). As DO_2 decreases, VO_2 is initially maintained because oxygen extraction is increased. At this point, VO_2 remains independent of DO_2, and the relationship is described as supply independent. Lactate remains normal, although $ScvO_2$ may begin to decline. As DO_2 continues to decline, oxygen extraction can no longer keep up with cellular demands and VO_2 falls precipitously. The critical DO_2 point (black dot) is passed the DO_2-VO_2 relationship becomes *supply dependent* (blue area) and represents physiologic deterioration. Biochemically, $SmvO_2$ falls as lactate rises

2.9 Summary

The physiology of oxygen transport and its manipulation have a central role in the management of the critically ill child. The pediatric critical care provider must have a keen understanding of the definitions, equations, and tools used to assess the adequacy of oxygen delivery. Oxygen delivery is primarily dependent on the hemoglobin concentration, the arterial oxygenation, and the cardiac output. The cardiac output is determined by the combined effects of preload, afterload, contractility, and heart rate. Oxygen consumption is influenced by many factors and may be reduced or increased in critical illness. A clear understanding of cellular respiration, oxygen delivery, and oxygen consumption is essential to the practice of pediatric critical care medicine.

Review Questions

1. Which statement is correct regarding the biochemical consequences of tissue hypoxia?
   - A. Anaerobic metabolism is as equally efficient as aerobic metabolism in producing energy but produces acid by-products such as lactate.
   - B. Elevated lactate levels can be readily buffered by the addition of sodium bicarbonate.
   - C. Lactate is produced as a by-product of anaerobic glycolysis during tissue hypoxia but may also be produced in the absence of tissue hypoxia.
   - D. Restoring tissue perfusion and oxygenation results in lactate being reconverted into glucose in the liver.
   - E. The reduction in pH seen during states of tissue hypoxia is primarily due to the accumulation of lactate.

2. A 16-year-old 50 kg male is admitted after correction of severe scoliosis and rib deformity that required a thoracotomy and chest tube placement. Upon admission, he is mildly tachycardic to 108 bpm, normotensive, and well perfused. His oxygen saturation is 99%, PaO_2 is 198 mm Hg on 50% FiO_2, and his hemoglobin is 10.9 g/dL.

You are called due to a steady increase in bloody chest tube output. He is now tachycardic to 149 bpm, has a blood pressure of 86/58 mm Hg, and is cool distally. His oxygen saturation is 87%, and PaO_2 is 65 mm Hg on 30% FiO_2.
Current hemoglobin is 7.6 g/dL.
What percent decrease in arterial oxygen content has occurred?

A. 10%
B. 15%
C. 30%
D. 40%
E. 50%

3. Rather than transfusing PRBC, you increase his FiO_2 to 60%. His PaO_2 increases to 120 mm Hg and SaO_2 to 100%.
You decide to calculate what the increase in CaO_2 would have been by transfusing PRBC to increase the hemoglobin from 7.6 g/dl to 9 g/dl without increasing the FiO_2.
Assume that after the transfusion, your PaO_2 would have increased slightly to 82 mm Hg and SaO_2 to 94%.
Which would have had a greater impact on CaO_2 and what was the best clinical correct approach?

4. Which of the following is true regarding oxygen-hemoglobin dissociation curve?
   A. Fetal hemoglobin increases oxyhemoglobin dissociation in the capillary circulation, thereby making more oxygen available at the tissue level.
   B. Hypoxemia increases oxyhemoglobin dissociation in the capillary circulation, thereby making more oxygen available at the tissue level.
   C. Increased temperature decreases oxyhemoglobin dissociation in the capillary circulation, thereby making less oxygen available at the tissue level.
   D. Severe acidosis decreases oxyhemoglobin dissociation in the capillary circulation, thereby making less oxygen available at the tissue level.
   E. Severe alkalosis decreases oxyhemoglobin dissociation in the capillary circulation, thereby making more oxygen available at the tissue level.

5. Which of the following is a true statement regarding physiologic determinants of oxygen delivery?
   A. Arterial oxygen content can be maximized, yet a state of decreased oxygen delivery may persist.
   B. Oxygen delivery is primarily determined by the rate of oxygen extraction.
   C. The determinants of cardiac output and the determinants of arterial oxygen content are different and have limited interdependence.
   D. The fractional inspired oxygen content impacts arterial oxygen content, and, therefore, oxygen delivery, more than the hemoglobin concentration.
   E. Therapies aimed at improving oxygen delivery are primarily related to maintaining alveolar oxygenation.

6. Which of the following is most correctly matched?
   A. Epinephrine .05 mcg/kg/min – decreased myocardial oxygen consumption.
   B. Low oxygen delivery – increased oxygen extraction.
   C. Cyanide poisoning – increased oxygen extraction.
   D. Neuromuscular blockade – increased oxygen consumption.
   E. Shivering – decreased oxygen consumption.

7. Which statement best reflects the ability of the body to extract oxygen?
   A. Baseline oxygen extraction varies among individual organs but remains constant during changes in clinical conditions.
   B. High oxygen extraction is reflected in a lower venous oxygen content.
   C. The normal oxygen extraction ratio (O_2ER) is approximately 50% of the oxygen being delivered to the tissues. The excess in delivered oxygen allows for an increase during stress states, thereby minimizing the need for anaerobic metabolism.
   D. Organs with lower metabolic demand will consume less oxygen and, consequently, will have a lower venous oxygen content.
   E. The oxygen extraction ratio (O_2ER) is determined by dividing the difference of the arterial and venous oxygen content by the cardiac output.

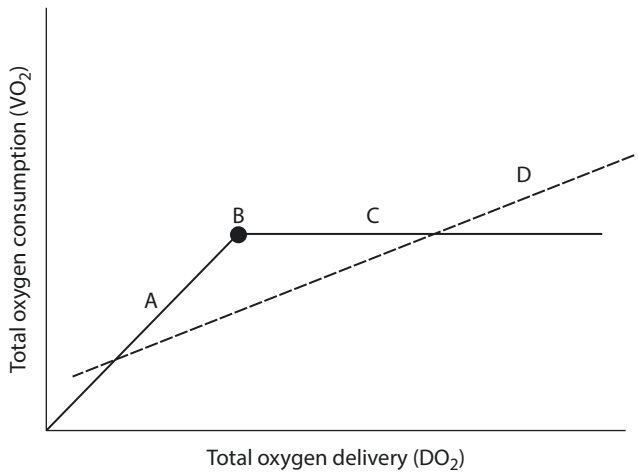
8. A 3-year-old presents with pallor, a murmur, and a heart rate of 140 bpm. He is afebrile and his pulse oximetry is 97%. There is no history of acute blood loss, but he consumes up to a liter of cow's milk per day. Laboratory analysis reveals a white blood cell count of 12, 300 cells/μL, hemoglobin of 4.5 g/dL, and a platelet count of 210,000/μL. His smear reveals microcytic and hypochromatic RBCs. He has a bicarbonate of 18 mmol/l. His arterial blood gas reveals pH 7.32, $PaCO_2$ 33 mm Hg, PaO_2 65 mm Hg, base deficit −9, and an oxygen saturation of 97%. The most appropriate next course of action is which of the following?
   A. Transfuse 15 mL/kg of packed red blood cells over 2 h.
   B. Transfuse 5 mL/kg packed red blood cells over 4 h and administer a dose of sodium bicarbonate.
   C. Transfuse 5 mL/kg packed red blood cells over 4 h and begin erythropoietin.
   D. Transfuse 5 mL/kg of packed red blood cells over 4 h and begin supplemental oxygen.
   E. Transfuse 15 mL/kg of packed red blood cells over 4 h and monitor for signs of pulmonary edema utilizing furosemide if necessary.

9. A 14-year-old multiple trauma victim with adult respiratory distress syndrome is admitted to the PICU. To optimize his care, you have placed an intravenous oximetric catheter with its tip in the superior vena cava to monitor venous oxygen saturation continuously. The patient is intubated, mechanically ventilated, and heavily sedated. His superior vena cava saturation has consistently been in the low 80 range but has suddenly begun to decrease into the low 70s. His pulse oximeter is unchanged and continues to read 99%. His vital signs are stable except for a fever spike up to 39.8 °C and a 5–10 beat increase in his heart rate. He remains heavily sedated on a midazolam infusion. The most likely explanation for his sudden decrease in superior vena cava saturation is which of the following?
   A. Acute occult blood loss
   B. Decreased cardiac output
   C. Increased metabolic demand
   D. Migration of the catheter into the right atrium
   E. Subclinical seizure

10. Hypoxemia is detected by special nerve chemical receptors located in the carotid and aortic bodies. When these chemoreceptors are triggered by hypoxemia (PaO_2 < 60 mm Hg, corresponding to SaO_2 < 93%), which of the following physiologic responses ensue?
    A. Stimulation of the respiratory area of the medulla resulting in a decrease in minute ventilation, respiratory pauses, and potentially apnea.
    B. Stimulation of the respiratory area of the medulla resulting in an increase in minute ventilation, a higher alveolar oxygen concentration (PAO_2), and, ultimately, an increase in the arterial oxygen content.
    C. Stimulation of the vasomotor center of the brainstem leading to decreased sympathetic tone and bradycardia.
    D. Stimulation of the vasomotor center of the brainstem resulting in decreased sympathetic tone, decreased metabolic rate, and decreased oxygen consumption.
    E. Stimulation of the vasomotor center of the brainstem resulting in increased sympathetic tone, increased systemic vascular resistance, and decreased cardiac output.

11. Of the organs listed, which pair represents the organ with the highest resting blood flow (mL/100 g/min) and the organ with the highest oxygen extraction ratio?
    A. Skin/heart
    B. Kidney/heart
    C. Muscle/heart
    D. Kidney/brain
    E. Splanchnic bed/brain

12. Which of the following labels best describe the graph?



    A. A = supply independent, B = supply dependent, C = pathologic DO_2
    B. A = supply dependent, C = supply independent, D = pathologic supply dependency
    C. A = supply dependent, B = pathologic supply dependency, C = supply independent
    D. A = supply independent, B = critical DO_2, D = supply dependent
    E. A = supply dependent, C = increased O_2 extraction, D = normal DO_2

13. Which definition and formula are incorrectly matched?
    A. Oxygen delivery: DO_2 (ml/min) = CO (L/min) × CaO_2 (mL/dL)
    B. Arterial oxygen content: CaO_2 (mL O_2/dL) = $Hgb_{gm/dl}$ × 1.34 × SaO_2 + (PaO_2 × .003)
    C. Arteriovenous oxygen content difference: avDO2 (mL O_2/dL) = CaO_2 – CvO_2
    D. Oxygen extraction ratio: O_2ER = (CaO_2 – CvO_2)/VO_2
    E. Oxygen consumption: VO_2 (mL O_2/min) = CO × (CaO_2 – CvO_2)

14. A 12-year-old male with relapsed ALL presents with septic shock that requires volume resuscitation and the institution of a norepinephrine infusion. He undergoes placement of a right radial arterial catheter and central venous catheter via the internal jugular vein. The tip of the catheter is at the SVC-right atrial junction.
    The following data is obtained:
    Hemoglobin 7.8 gm/dL, PaO_2 85 mm Hg, SaO_2 92%. Lactate 5.5
    Blood drawn from the CVP reveals: PvO_2 30 mm Hg and SvO_2 56%
    What is the $avDO_2$?
    A. 3.9 mL O_2/dL
    B. 5.3 mL O2/dL
    C. 5.5 mL O_2/dL
    D. 6.3 mL O_2/dL
    E. 6.8 mL O_2/dL

15. Using the same data, calculate the oxygen extraction ratio.
    A. 20%
    B. 30%
    C. 40%
    D. 50%
    E. 55%

Answers

1. C
2. D Decreasing from 15 to 9, our patient lost 40% of CaO_2.
   CaO_2 = 10.9 gm/dL × 1.34 mL O_2/gm Hgb × .99 + (198 × .003) = 15.06
   CaO_2 = 7.6 gm/dL × 1.34 mL O_2/gm Hgb × .87 + (65 × .003) = 9.06
3. The patient had symptomatic anemia from acute blood loss. Increase the FiO_2 while awaiting transfusion.
   Increasing FiO_2 to 100% and no transfusion:
   CaO_2 = 7.6 gm/dL × 1.34 mL O_2/gm Hgb × 1+ (120 × .003) = 10.5
   Transfusion to 9 gm/dL and no FiO_2 increase:
   CaO_2 = 9 gm/dL × 1.34 mL O_2/gm Hgb × .94 + (82 × .003) = 11.5
4. B
5. A
6. B
7. B
8. D
9. C

10. B
11. B
12. B
13. D
14. A CaO_2 = 7.8 gm/dL × 1.34 mL O_2/gm Hgb × .92 + (85 × .003) = 9.85
    CvO_2 = 7.8 gm/dL × 1.34 mL O_2/gm Hgb × .56 + (30 × .003) = 5.94
    9.85–5.94 = 3.9
15. C 9.85–5.94/9.85 = 40%

Suggested Reading

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Endothelial Interactions and Coagulation

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Contents

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3

Learning Objectives

- Describe the components of the soluble coagulation/fibrinolysis system.
- Describe how the endothelium and coagulation/fibrinolysis system promote blood flow without clotting.
- Describe how the endothelium and coagulation/fibrinolysis system stops bleeding and promotes healing after focal vascular injury.
- Describe endothelium and platelet/von Willebrand factor hemostatic system pathophysiology in thrombotic thrombocytopenic purpura.
- Describe endothelium and fibrin coagulation system pathophysiology in consumptive disseminated intravascular coagulation (DIC).
- Describe endothelium, complement system, platelet/von Willebrand factor hemostatic system, and fibrin coagulation system pathophysiology in hemolytic uremic syndrome (HUS).
- Describe endothelium, platelet, and fibrin coagulation system pathophysiology in nonconsumptive secondary thrombotic microangiopathy.
- Describe endothelium, platelet, and fibrin coagulation pathophysiology in bleeding disorders, including von Willebrand's disease, severe trauma, hemophilia, liver failure, and uncontrolled DIC.
- Describe diagnostic tools to assess the presence and cause of pathologic thrombosis and bleeding.
- Describe the pros and cons of using specific and nonspecific therapies to reverse thrombosis and/or bleeding disorders in critically ill children.

3.1 Introduction

Circulating blood is the lifeline of our existence, transporting oxygen, glucose, and other substrates for energy production. The circulatory system supplies complements, platelets, and white blood cells to combat infections and repair tissues, as well as platelets and soluble coagulation and anticoagulation proteins and proteases, to prevent uncontrolled bleeding and clotting. The coordination of these vital functions is orchestrated by a thin layer of cells named the endothelium. Endothelial cells direct blood flow by differentially expressing vasoconstrictors (e.g., endothelin, 20-HETE) and vasodilators (e.g., nitric oxide, prostacyclin). These cells direct white blood cell trafficking by differentially expressing the adhesion molecules endothelial selectin (E-selectin), intercellular adhesion molecule (ICAM), and vascular cell adhesion molecule (VCAM). Finally, the endothelium directs clotting by differentially releasing ultra-large von Willebrand factor (ULVWF) multimers (initiating platelet aggregation), decreasing thrombomodulin (preventing anticoagulation), and increasing plasminogen-activator inhibitor type-1 (PAI-1) expression preventing fibrinolysis. This chapter focuses on the physiology and pathophysiology of the endothelium and the cellular and soluble coagulation and complement systems. The objective of this chapter is to prepare the pediatric intensivist to choose specific and nonspecific therapies for critically ill children with thrombotic and/or bleeding disorders.

3.2 Endothelial Interactions and Coagulation

Coagulation is mediated by complex interactions between platelets, endothelium, and the soluble proteins and proteases.

Coagulation is mediated by complex interactions between platelets, endothelium, and the soluble proteins and proteases. This system has a dual function maintaining the balance between systemic pro-coagulation and anticoagulation, which prevents systemic bleeding and clotting, but also directing platelet and fibrin clotting to areas of focal endothelial injury when endothelial and vascular injury occurs. The many soluble components of the fibrin coagulation

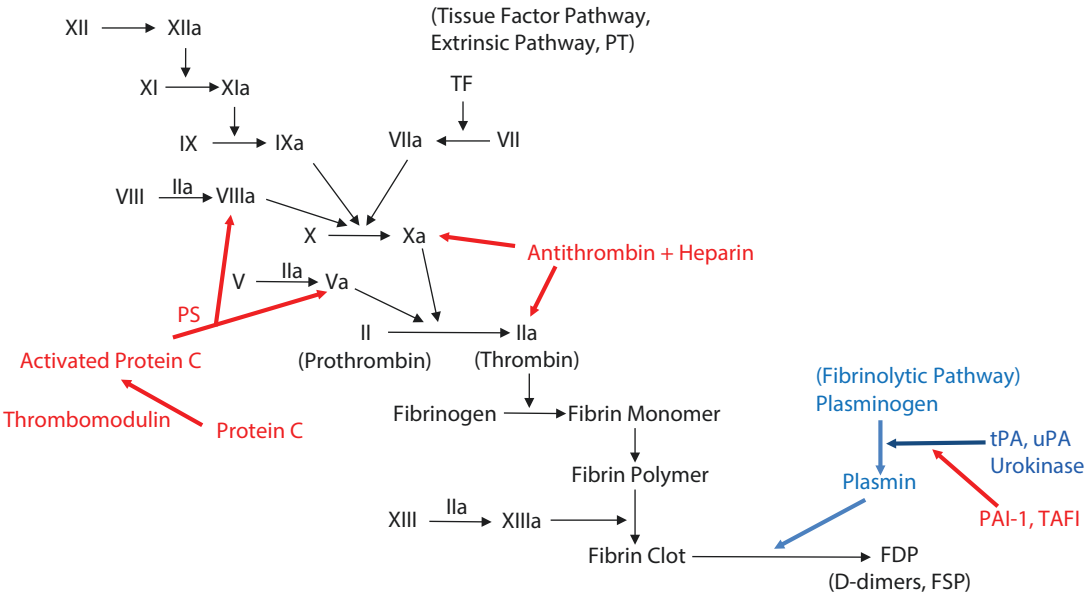

Fig. 3.1 The fibrin coagulation and fibrinolysis cascade coagulation

system are represented in Fig. 3.1. For the most part, the active enzymes in this system are serine proteases, which are produced in the liver. However, factor VIII, thrombomodulin, plasminogen activator inhibitor type-1, prostacyclin, and von Willebrand factors (VWF) are produced in the endothelium. Tissue factor is an important molecule because it is the initiator of the coagulation cascade. Thrombin (factor IIa) is the most important molecule and the final common pathway in the clotting cascade. The conversion of circulating prothrombin (factor II) into thrombin catalyzes the transformation of fibrinogen into a fibrin clot. It also activates the thrombin activatable fibrinolysis inhibitor (TAFI), which reduces the production of plasmin, inhibits fibrinolysis, and preserves the fibrin clot. Plasmin is the most important molecule in the fibrinolytic pathway. Conversion of circulating plasminogen into plasmin, the mediator of fibrinolysis, is controlled by endogenous plasminogen activator activity, including tissue plasminogen activator (tPA) in the plasma and uroplasminogen activator (uPA) in the ureters and bladder. The plasminogen activators are directly inhibited by plasminogen activator inhibitor type-1 (PAI-1). Protein C (in concert with thrombomodulin), protein S, tissue factor pathway inhibitor, antithrombin III, and heparin are the major anticoagulant proteins.

Under conditions of homeostasis, blood flows unimpeded by clotting because the endothelium, platelets, and soluble coagulation system are in the anticoagulant state (Fig. 3.2). The endothelium expresses prostacyclin and nitric oxide, which prevent platelet aggregation; tPA, which activates plasminogen to plasmin which lyses fibrin clots; and thrombomodulin, which converts protein C to activated protein C, which prevents thrombin generation and inhibits plasminogen activator inhibitor type-1, promoting fibrinolysis at the endothelium surface. Circulating endogenous heparin complexes with antithrombin III, further preventing systemic fibrin generation. Tissue factor pathway inhibitor, which also circulates through the vascular system, complexes with released tissue factor and inhibits factor VII-mediated coagulation. During homeostasis, the anticoagulant state is balanced with adequate levels of prothrombotic coagulation factors so that bleeding does not occur.

Thrombin (factor II a) is the most important molecule and the final common pathway in the clotting cascade.

Protein C (in concert with thrombomodulin), protein S, tissue factor pathway inhibitor, antithrombin II, and heparin are the major anticoagulant proteins.

When focal vascular injury occurs by way of trauma, the coagulation system directs a platelet and fibrin clot to the site while maintaining the systemic anticoagulant state.

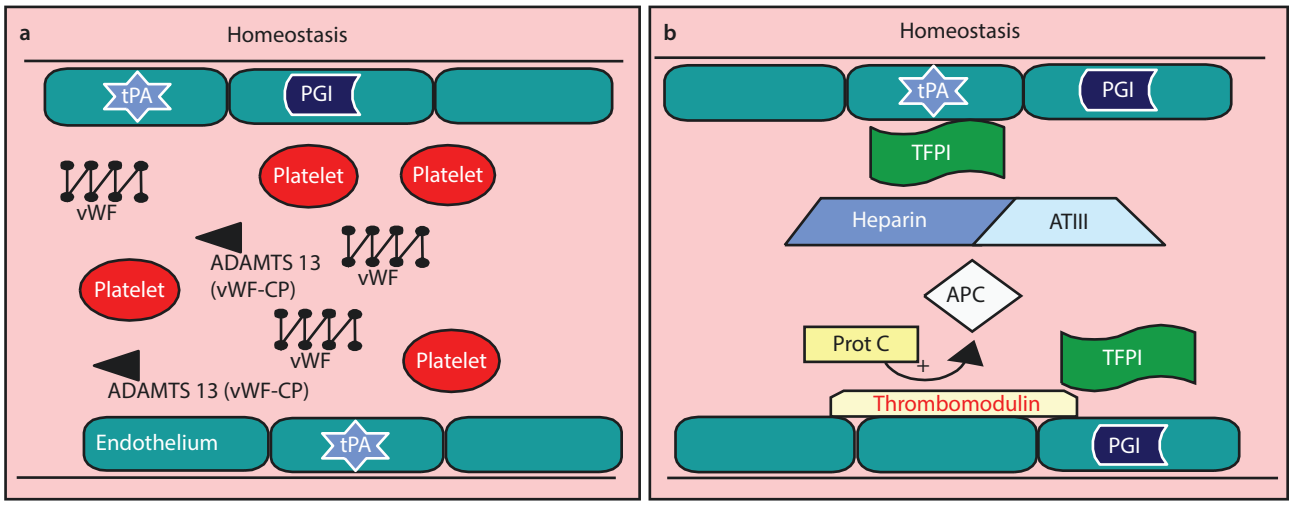

Fig. 3.2 Homeostasis is maintained by a platelet **a** and fibrin **b** anticoagulant state. *PGI* prostacyclin, *tPA* tissue plasminogen activator, *ADAMTS-13* (VWF-cleaving protease), *VWF* von Willebrand factor multimers, *TFPI* tissue factor pathway inhibitor, *APC* activated protein C, *ATIII* antithrombin III

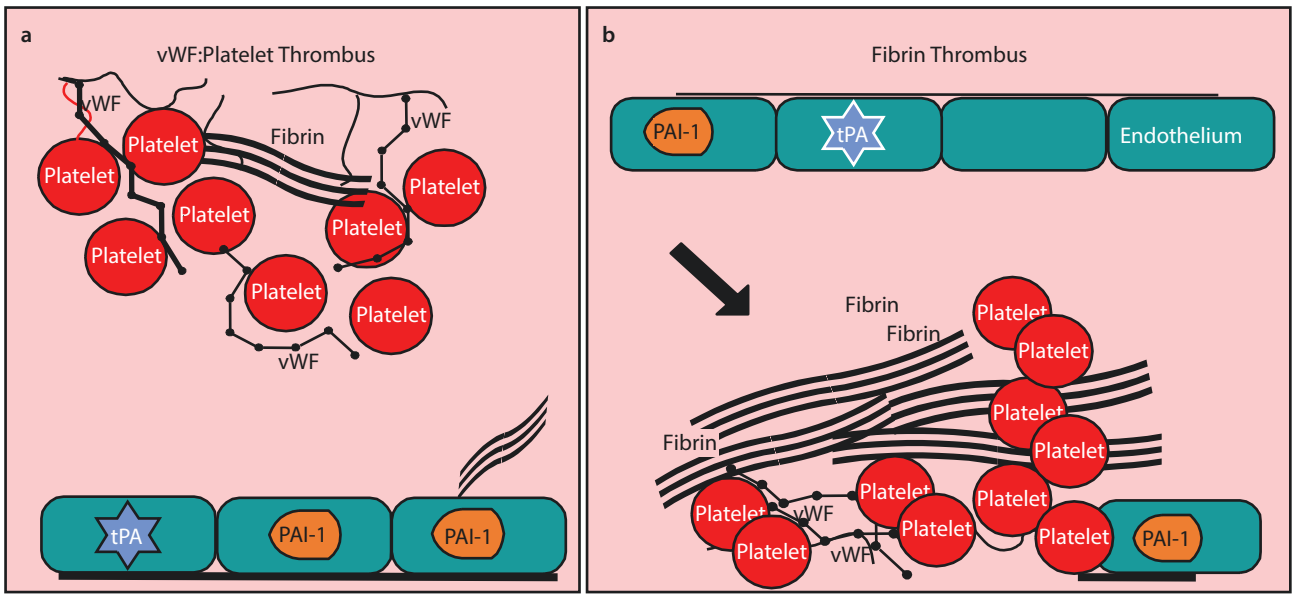

Fig. 3.3 Focal injury is repaired by a directed platelet and fibrin thrombus, which develops locally, while the anticoagulant state is maintained systemically. PAI-1 plasminogen activator inhibitor

During infection, fibrin thrombosis occurs because IL-1 and TNF-a decrease endothelial thrombomodulin expression, preventing activation of the anticoagulant protein C.

When focal vascular injury occurs by way of trauma, the coagulation system directs a platelet and fibrin clot to the site while maintaining the systemic anticoagulant state (Fig. 3.3). This occurs in three steps: vasoconstriction, platelet aggregation, and fibrin deposition. The endothelial disruption results in the release of the vasoconstrictor endothelin and the absence of the vasodilators nitric oxide and prostacyclin. The net effect of this loss of balance in vasomotor control is vasoconstriction and stasis. The injured endothelium releases ultra-large VWF multimers. These hyper-adhesive ultra-large VWF multimers initiate platelet aggregation and form the platelet plug at the site of the endothelial disruption. The loss of endothelium at this site exposes tissue factor in the absence of thrombomodulin. The fibrin clot is formed through the activation of factor VII by tissue factor in the absence of activated protein

C. Thrombin activates TAFI at the site, and the surrounding endothelium increases plasminogen activator inhibitor type-1, preventing fibrinolysis of the mature clot. Although the site of injury is in a procoagulant and antifibrinolytic state, the systemic endothelium and circulating system remain in an anticoagulant state. The focal clot is formed without systemic clotting. When the vascular injury is repaired and the endothelium is regenerated, the local anticoagulant state is restored and the focal clot is lysed.

Critically ill patients develop a systemic endothelial microangiopathic process, leading to thrombotic microangiopathy after many types of systemic insults.

When focal vascular injury occurs by way of infection, the coagulation system also directs a platelet and fibrin clot to the site while maintaining the systemic anticoagulant state (■ Fig. 3.3). This occurs in three steps: vasodilation (not vasoconstriction), platelet aggregation, and fibrin deposition. This process is mediated by cytokine production from immune cells, endothelium, vascular smooth muscle cells, and surrounding tissues. Nitric oxide is increased leading to local vasodilation with increased blood flow. The cytokines, IL-1, TNF-α, and IL-6 mediate focal thrombosis. The cytokines induce adhesion molecule expression in the endothelium (E-selectin, ICAM, and VCAM), which direct white blood cells and platelets to the site of injury. Platelet aggregation occurs because TNF-α, IL-6, and IL-8 stimulate the release of the hyper-adhesive ultra-large VWF multimers and inhibit the activity of the ADAMTS-13 (VWF-cleaving protease). Fibrin thrombosis occurs because TNF-α induces monocytes to release tissue factor, which activates coagulation, while IL-1 and TNF-α decrease endothelial thrombomodulin expression, preventing activation of the anticoagulant protein C. These cytokines also increase endothelial expression of plasminogen activator inhibitor type-1 (PAI-1), which prevents lysis of the clot. When the infection resolves, cytokine production stops and ADAMTS-13 activity is restored, tissue factor is not released, thrombomodulin expression is increased, and PAI-1 expression is decreased. The clot dissolves as increased ADAMTS-13 and thrombomodulin activity prevent further thrombosis and absent PAI-1 activity allows endogenous tPA fibrinolysis to proceed. As in the case of focal traumatic vascular injury, the systemic circulation remains in the anticoagulant/pro-fibrinolytic state during the entire process. The link between killing infection and promoting thrombosis is evident. Platelets both induce coagulation and release endogenous antimicrobial peptides, which destroy bacteria and fungi, and monocytes/macrophages both kill infection and release tissue factor, which induces fibrin clotting. During homeostasis, the coagulation system allows blood to flow unimpeded without clotting. During focal vascular injury caused by trauma or inflammation/infection, the endothelium changes phenotype to a procoagulant/hypo-fibrinolytic phenotype, which directs clotting at the site of injury, while maintaining an anticoagulant/pro-fibrinolytic phenotype outside of the locus of injury.

Prothrombotic and antifibrinolytic responses, which are helpful during focal injury, become injurious in the setting of systemic endothelial injury and are manifested by thrombocytopenia, systemic thrombosis, and multiple organ failure. Critically ill patients develop a systemic endothelial microangiopathic process, leading to thrombotic microangiopathy following many types of systemic insults (▶ Box 3.1). The pathophysiology of these thrombotic microangiopathic diseases induced by systemic endothelial injury can be characterized as part of a spectrum of four phenotypes: thrombotic thrombocytopenic purpura (TTP) (■ Fig. 3.4), consumptive disseminated intravascular coagulation (DIC) (■ Fig. 3.5), hemolytic uremic syndrome (HUS), and nonconsumptive secondary thrombotic microangiopathy (2° TMA) (■ Fig. 3.6).

3

Conditions associate with thrombotic microangiopathy

- Cancer
- Transplantation
- Cardiovascular surgery/cardiopulmonary bypass
- Autoimmune disease
- Systemic infection
- Vasculitis
- Toxins
- Cyclosporine A
- Tacrolimus
- Chemotherapy
- Radiation
- Ticlopidine

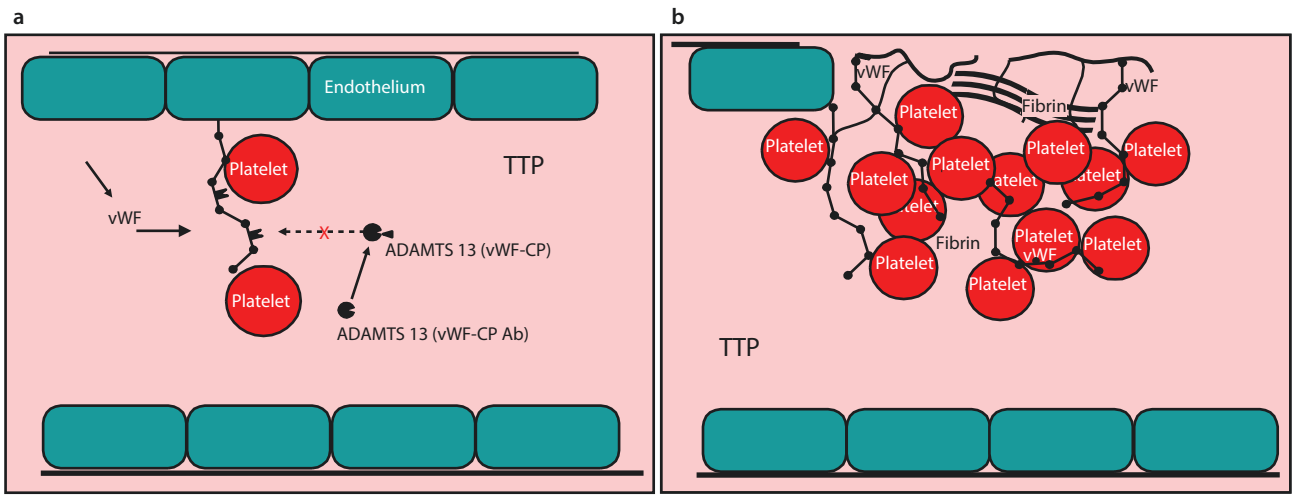

Fig. 3.4 Systemic inflammation results in systemic coagulation. Thrombotic thrombocytopenic purpura is a phenotype caused by ADAM TS-13 deficiency

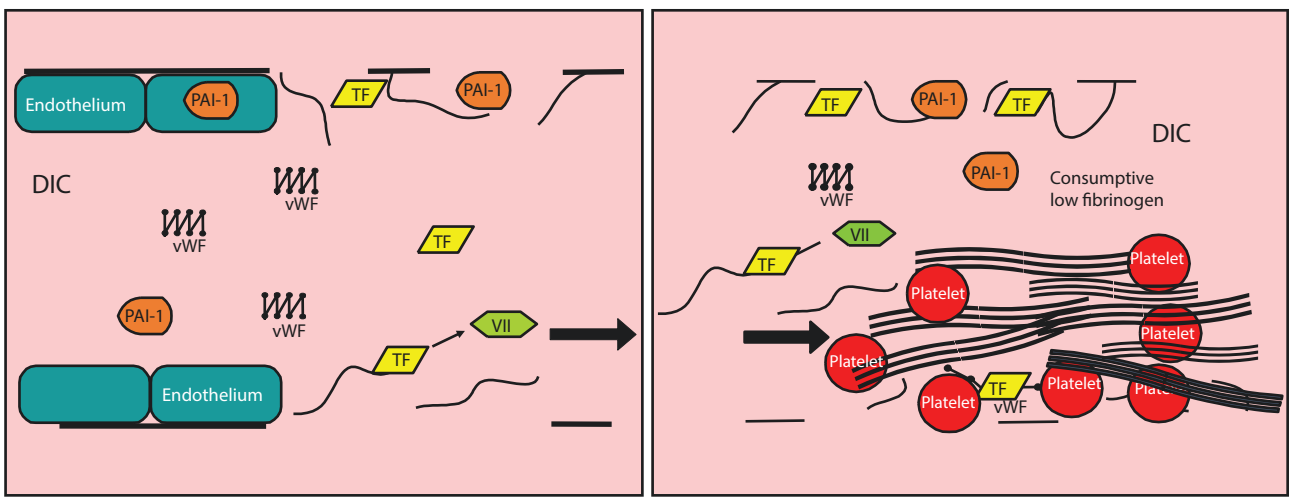

Fig. 3.5 Disseminated intravascular coagulation is a phenotype caused by increased tissue factor and PAI-1, unopposed by the anticoagulant proteins TFPI, protein C, AT III, and prostacyclin

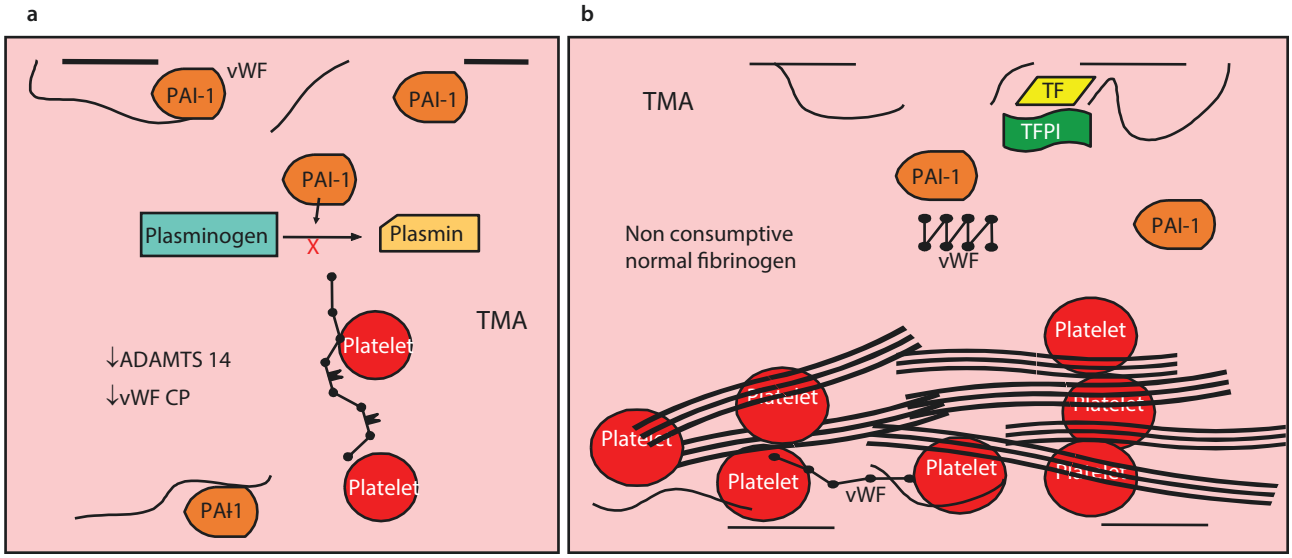

Fig. 3.6 Secondary thrombotic microangiopathy, caused by systemic endothelial injury, shares the TTP phenotype with deficient ADAMTS-13 and increased PAI-1 levels

The complement system needs to be mentioned, because it is functionally involved with endothelial interactions and coagulation. The complement system is essential for our immune response, as it acts as an effector of humoral defense against invading pathogens. However, when the complement system becomes dysregulated and overactive, it can lead to uncontrolled systemic inflammation and disseminated microvascular thrombosis due to the pathologic interactions, among the complement proteins, endothelium, platelet/VWF, and fibrin pathways. The complement system is tightly regulated to be activated on pathogen surfaces with limited deposition of complement proteins on normal host cells. This system comprises more than 30 components, which include serum protein and cell-surface molecules. There are three activation pathways: (1) the classical pathway, (2) the lectin pathway, and (3) the alternative pathway, which involves the direct activation of C3 through surface binding. Activations of complement will lead to generation of C3b by C3 convertases with the formation of the membrane attack complex (MAC, C5b-9). This MAC forms transmembrane channels, which disrupt cell membrane of target cells, leading to cell lysis and death.

Disseminated intravascular coagulation is a consumptive syndrome, consuming procoagulant factors such as fibrinogen.

Thrombotic thrombocytopenic purpura (TTP) has been described in two forms, acute and chronic relapsing. The classic "pentad" of TTP is composed of the constellation of fever, thrombocytopenia, abnormal mental status (with or without seizures), renal dysfunction, and microangiopathic hemolysis, indicated by an elevated lactose dehydrogenase (LDH) level and/or the presence of schistocytes. The acute form, which accounts for the majority of cases, occurs when ADAMTS-13 inhibitors and proteolytic inactivators develop, leading to acquired ADAMTS-13 deficiency. There is a growing list of ADAMTS-13 inhibitors, all of which are elevated during systemic inflammation and activated coagulation, including interleukin-6, granulocyte elastase, human neutrophil peptides, plasmin, thrombin, plasma free hemoglobin, Shiga toxin, and IgG autoantibodies (Fig. 3.4). This decrease in VWF cleaving proteinase activity results in an inability to cleave ultra-large and large VWF multimers to their smaller, less thrombogenic VWF multimers. VWF multimers have binding sites

to collagen and platelets. Because these antibodies are produced in the presence of disease states associated with increased shear stress, the circulating ultra-large VWF multimers unfold and spontaneously aggregate platelets, leading to disseminated VWF/platelet-rich microthrombi. The less common but chronic relapsing form of TTP occurs in patients with congenital deficiency of ADAMTS-13. These patients become ill during periods of systemic illness associated with increased microvascular shear stress. Fibrin thrombosis is involved as well. There is a reduction in tissue factor pathway inhibitor (TFPI) levels without an increase in tissue factor levels (TF) and an increase in PAI-1 levels.

In the setting of the thrombotic form of a DIC, a prolonged PT/aPTT may occur in the setting of a procoagulant rather than an anticoagulant state.

Disseminated intravascular coagulation (DIC) is a consumptive syndrome (consuming procoagulant factors such as fibrinogen) which is represented in its most severe form by purpura fulminans and in its least severe form by abnormalities in the platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT). Disseminated intravascular coagulation is described as the constellation of thrombocytopenia, decreased factors V and VIII, decreased fibrinogen, and increased D-dimers. The depletion of factors and fibrinogen explains the common association with prolongation of the PT and aPTT. Two phenotypes of DIC have been recognized; one is associated with a predominant bleeding diathesis, and the other with disseminated systemic thrombosis. The most common causes of the thrombotic/hemorrhagic phenotypes include virus-induced hemorrhagic fevers, severe brain tissue disruption, and promyelocytic leukemia. The most common causes of the thrombotic phenotype are bacterial and fungal infections.

The tissue factor: factor VII pathway, not the factor XII pathway, is responsible for the prothrombotic form of DIC caused by systemic bacterial infection.

There has been a significant improvement in the understanding of the thrombotic form of DIC syndrome in recent years. In diagnosing the thrombotic process, it is important to understand the manner in which increased coagulation occurs despite prolongation of the PT/aPTT. Traditionally, prolongation of the PT/aPTT and reduced platelet counts are indicative of a greater tendency to bleeding. However, in the setting of the thrombotic form of a DIC, a prolonged PT/aPTT may occur in the setting of a procoagulant rather than an anticoagulant state. It appears counterintuitive for clinicians to recommend heparin therapy for patients with DIC when the patient has thrombocytopenia and a prolonged PT/aPTT.

Protein C, protein S, and antithrombin II are significantly reduced in patients with DIC.

Prothrombin time and aPTT are dependent on coagulation factors and fibrinogen. Prothrombin time and aPTT increase when these proteins are reduced and decrease when these proteins are increased. The tissue factor: factor VII pathway, not the factor XII pathway, is responsible for the prothrombotic form of DIC caused by systemic bacterial infection. When released into the circulation by monocytes or exposed by injured endothelium, tissue factor complexes with factor VII and initiates thrombosis (Fig. 3.5). If tissue factor promotes consumption of clotting factors to the point that factors V, factor VIII, and fibrinogen are depleted, the patient develops a prolonged PT/aPTT.

The endogenous anticoagulant system is also reduced and contributes to the thrombotic form of DIC. Protein C, protein S, thrombomodulin, and antithrombin III are significantly reduced in patients with DIC. Newborns with a congenital absence of protein C, protein S, or antithrombin III can develop spontaneous purpura fulminans, which is fatal if not treated with replacement of the anticoagulant proteins with fresh frozen plasma infusion (Table 3.1). The response of the antithrombotic system in systemic hemorrhagic fevers (dengue, Ebola, Korean, etc.), which are the leading cause of DIC in children in the Africa and Asian continents, is similar to that observed in meningococcemia in the Western world.

Table 3.1 Effect of nonspecific therapy on coagulation and fibrinolysis

Plasma infusion	Plasma exchange
Restores procoagulant factors	Restores procoagulant factors homeostasis
Restores anticoagulant factors (protein C, ATIII, TFPI)	Restores anticoagulant factor homeostasis (protein C, AT III, TFPI)
Restores prostacyclin	Restores prostacyclin homeostasis
Restores tPA	Restores tPA homeostasis
Restores ADAM TS-13	Restores ADAM TS-13 homeostasis
	Removes ADAMTS-13 inhibitors
	Removes ultra-large VWF multimers
	Removes tissue factor
	Removes excess PAI-1

The majority of patients with thrombotic microangiopathy have thrombocytopenia-associated multiple organ failure with a normal or mildly elevated PT/aPTT.

The antifibrinolytic system is predominant in patients with the thrombotic form of DIC. Tissue plasminogen activator levels initially increase. However, within 12–24 h, patients develop increased PAI-1 antigen levels and decreased plasmin α_2-antiplasmin production indicative of a hypo-fibrinolytic state. Children with meningococcal disease-associated purpura fulminans have increased PAI-1 antigen levels. The PAI-1 4G/5G promoter genetic polymorphism is associated with increased PAI-1 antigen levels and worse outcomes in children with meningococcal disease.

Hemolytic uremic syndrome (HUS) is a clinical "triad" of thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure. The underlying pathology of HUS is uncontrolled complement activation. HUS is divided into two major types, (1) infection-induced HUS, which includes Shiga toxin-producing *Escherichia coli* (STEC) and accounts for 90% of all HUS cases, and (2) atypical HUS, which includes genetic and acquired disorders of complement regulation and accounts for 10% of all HUS cases. The kidneys are the most common organ affected, but the brain and other organs can also be involved in severe cases. HUS patients suffer from overactive complement activation, deposition of complement proteins on various organs, disseminated microvascular thrombosis, and multiple organ failure.

Shiga toxin can bind to glycosphingolipid surface receptor globotriaosylceramide expressed on renal and brain endothelium. Shiga toxin can activate the complement system by (1) directly activating the alternative pathway, (2) releasing red blood cell microvesicles coated with MAC, (3) forming soluble MAC in blood, and (4) inhibiting factor H, which is an inhibitor of the alternative pathway. For atypical HUS, complement genetic pathway mutations account for 50–60%, and thrombomodulin mutations accounts for 5% of cases.

The linkage between the complement pathway, the endothelium, and coagulation is as follows. During systemic inflammation, the endothelium releases both the alternative complement proteins and ULVWF. ULVWF then anchors on the surface of the endothelium, where complement proteins are assembled, activated, and form MAC. MAC then causes local destruction of the endothelium. Shiga toxin can inhibit ADAMTS-13 and activate the endothelium to release both alternative complement proteins and ULVWF. Again, this leads to MAC formation and local endothelial injury. Shiga toxin also causes shedding of thrombomodulin from the endothelial surface, leading to less protein C activation and a prothrombotic state.

The clinical tests presently used to diagnose thrombosis or bleeding are not very effective.

Nonconsumptive secondary thrombotic microangiopathy occurs in critically ill patients with secondary TTP/HUS syndrome (Fig. 3.6). It is identified clinically by the constellation of criteria present with the primary form of thrombotic microangiopathy, TTP, with the exception that there is no evidence of hemolysis on the peripheral smear. The majority of patients with thrombotic microangiopathy have thrombocytopenia-associated multiple organ failure with a normal or mildly elevated PT/aPTT. These patients have increased or normal factor V, VIII, and X and fibrinogen levels but also have increased D-dimers. These children have thrombogenic ultra-large VWF multimers, ADAMTS 13 deficiency, circulating ADAMTS-13 inhibitors and increased PAI-1 but normal TFPI activity and TF activity (Fig. 3.6). The systemic endothelium is in a platelet procoagulant and fibrin antifibrinolytic state, but in contrast to DIC, it is not in a fibrin procoagulant state. Hence, consumption of procoagulant factors is not observed to the degree noted during DIC. This pathophysiologic process has been observed and described in patients with severe meningococcal sepsis, severe sepsis, severe malaria, thrombocytopenia-associated multiple organ failure, and hepatic veno-occlusive disease after stem cell transplantation.

Critically ill patients commonly have reduced anticoagulant proteins as well as procoagulant proteins.

Systemic bleeding can occur in critically ill patients with systemic endotheliopathy. In patients with TTP, DIC, or 2° TMA, bleeding occurs when too few platelets or procoagulant factors are left in the circulation to maintain hemostasis. Similarly, in patients with liver disease, coagulation disorders, such as von Willebrand disease or hemophilia, or exsanguinating trauma, there are too few functional platelets or procoagulant factors available to provide hemostasis. Moreover, excessive fibrinolysis can also result in bleeding. For example, certain microorganisms secrete fibrinolytic factors, varieties of snakes secrete venoms with prothrombotic and fibrinolytic factors, and some chemotherapeutic agents induce thrombosis and fibrinolysis, which result in bleeding. Therefore, the pediatric intensive care physician must be cognizant of both systemic thrombosis and bleeding in critical illness.

The clinical tests presently used to diagnose thrombosis or bleeding are not very effective (Tables 3.2 and 3.3). Thrombocytopenia may be a sign of proclivity to bleeding but may also be a sign of systemic thrombosis. Idiopathic thrombocytopenic purpura (ITP) presents with purpura and a bleeding risk, when platelet counts are <20,000/μL. When ITP is associated with platelet counts <10,000/μL, patients are at an increased risk of intracranial hemorrhage. However, new-onset thrombocytopenia and multiple organ failure are the hallmark of disseminated microvascular thrombosis in patients with TTP, DIC, HUS, or 2° TMA. The PT/aPTT and the international normalized ratio (INR) are also used as indicators of bleeding risk, particularly in patients with hemophilia who are deficient in specific procoagulant proteases. However, critically ill patients commonly have reduced anticoagulant proteins as well as procoagulant proteins. In these patients, prolonged PT/aPTT can be a sign of systemic thrombosis. The child with fulminant hepatic failure requiring transplantation illustrates this paradox. Before transplantation, the prolonged PT/aPTT is often associated with a proclivity to bleeding (greater reduction in procoagulant then anticoagulant factors). However, following transplantation, the prolonged PT/aPTT is associated with a greater proclivity to thrombosis (greater reduction in anticoagulant than procoagulant proteins).

There are two uncommonly used clinical tests that can be used to determine systemic clotting and fibrinolysis. With every thrombin molecule produced, the prothrombin activation fragment 1.2 (F1.2) is generated. Increased levels F1.2 levels are indicative of systemic thrombosis. When each fibrin monomer is lysed by plasmin, there is consumption of a plasmin α2-antiplasmin molecule. Increased plasmin α2-antiplasmin levels are associated with hypofibrinolysis and systemic clotting, and decreased levels are associated with increased fibrinolysis and systemic bleeding.

Table 3.2 Diagnostic criteria and treatment recommendations for thrombotic disorders

Diagnostic criteria	Treatment
TTP	*TTP*
Fever	(a) Steroids × 24 h
Thrombocytopenia	(b) Within 30 h perform 1.5 volume plasma exchange then 1 volume daily until resolution of thrombocytopenia (median 18 days)
Increased LDH	(a) If recalcitrant use cryopreserved supernatant
Schistocytes >5%	(b) If refractory, consider rituximab or vincristine
Neurologic and renal dysfunction	
DIC	*DIC*
Thrombocytopenia	(a) Reverse shock and underlying disease (increase flow with fluids and consider vasodilators – nitroglycerin, milrinone, pentoxifylline)
Decreased factors V, VIII, and X and fibrinogen	(b) Replace clotting factors with FFP, cryoprecipitate, and platelets via plasma infusion or plasma exchange
Decreased antithrombin III and protein C	(c) Anticoagulate with heparin, protein C, or antithrombin III, prostacyclin
Increased D-dimers	(d) Use fibrinolytics for life- or limb-threatening thrombosis. Remember to keep PT/aPTT and platelets normal when giving fibrinolytics
Prolonged PT/aPTT	(e) Give antifibrinolytics if life-threatening bleeding (rarely needed when PT/aPTT and platelet counts are maintained)
HUS	*HUS*
Thrombocytopenia Hemolytic anemia Acute kidney injury Complement activation	(a) Anti-C5 antibody (eculizumab) for atypical HUS (unclear role for STEC HUS) (b) Plasma exchange for autoantibody mediated HUS (factor H autoantibody) (c) Consider plasma exchange for non-autoantibody-mediated HUS
2° Thrombotic microangiopathy	*2° Thrombotic microangiopathy*
Thrombocytopenia	(a) Remove source of 2°TMA
Increased LDH	(b) Plasma exchange for adult severe sepsis (median 3 days) and for children with thrombocytopenia-associated multiple organ failure
Normal or elevated fibrinogen	(c) TTP-based plasma exchange protocol for children (see above) until resolution of thrombocytopenic multiple organ failure (median 12 days)
<5% schistocytes	
Multiple organ failure	

In terms of therapy, there is an array of nonspecific and specific therapies available to the intensivist for management of the critically ill child with disseminated microvascular thrombosis and bleeding (Fig. 3.7). Thrombotic thrombocytopenic purpura mortality was almost uniform before the use of corticosteroids and plasma exchange therapy, which significantly reduced TTP

There is an array of nonspecific and specific therapies available to the intensivist for management of the critically ill child with systemic thrombosis and bleeding.

Table 3.3 Diagnostic criteria and treatment recommendations for bleeding disorders

Diagnostic criteria	Recommended therapy
Trauma	*Trauma*
Bleeding from sites of trauma	(a) Surgical hemostasis
Prolonged PT/PTT	(b) Platelet and procoagulant factor replacement
Thrombocytopenia	(c) Activated factor VII can be effective when this fails
	(d) Aminocaproic acid reduces bleeding during ECMO
Liver failure	*Liver failure*
Decreased factor II, VII, IX	(a) Vitamin K
	(b) Platelet and procoagulant factor replacement
	(c) Activated factor VII can be effective when this fails
Congenital coagulant deficiency	*Congenital coagulation deficiency*
Deficient factor VII, factor VIII, factor IX, von Willebrand factor	(a) In the absence of consumption (DIC), 30 mL/kg of FFP (FVII, VIII, IX, VWF) or cryoprecipitate (FVIII, IX, VWF) corrects these deficiencies
	(b) Specific concentrates are available and effective
	(c) Activated concentrates should be used when bleeding is life-threatening (caution: can cause thrombosis)

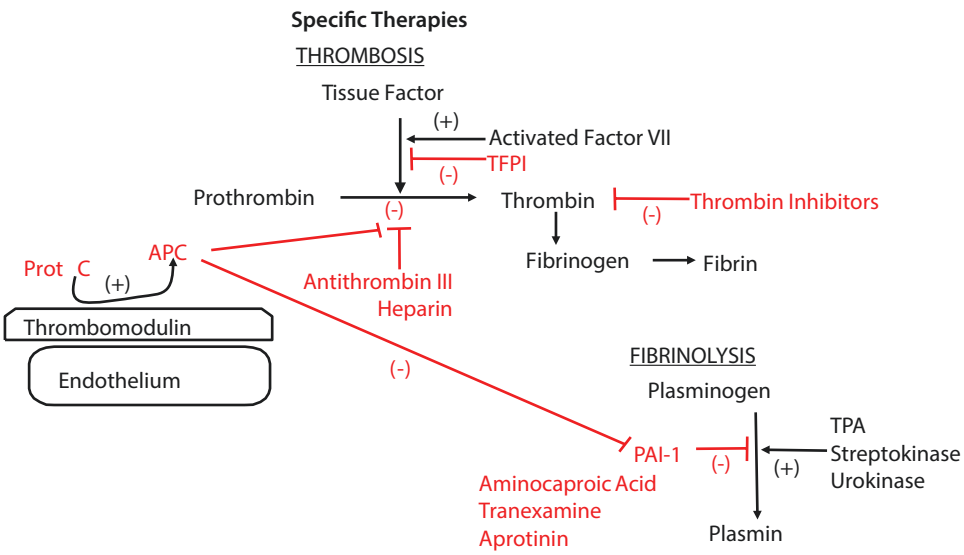

Fig. 3.7 Specific therapies used to **a** reverse thrombosis (*Pro C* = protein C concentrate, *APC* = activated protein C, *TFPI* = tissue factor pathway inhibitor, antithrombin III, heparin, thrombin inhibitors (such as argatroban and hirudin), **b** promote thrombosis (*activated factor VII*) and **b** promote fibrinolysis (*TPA* = tissue plasminogen activator, streptokinase, urokinase, defibrinopeptide), or **c** stop fibrinolysis (aminocaproic acid, tranexamine, aprotinin)

mortality. Interestingly, many of these patients treated in this way had evidence of DIC. Histology in these patients also demonstrated fibrin-rich microthrombi and inflammatory cell lesions compared to the pathognomonic platelet/VWF-rich microthrombi in TTP. These patients were defined as having TTP by a

process of elimination when no other causes (e.g., infection, toxin, autoimmune disease) could be found to explain the underlying microangiopathy. The presence of an underlying process excluded the diagnosis of TTP. In contrast, plasma exchange (median of 18 days) appears superior to plasma infusion in improving survival in patients with TTP with a normal PT/aPTT.

Plasma exchange appears superior to plasma infusion in improving survival in patients with TTP with a normal PT/aPTT.

Acute TTP can be treated successfully. As the process can be mediated by antibodies or other inhibitors to ADAMTS-13, a trial of steroid therapy is reasonable as a first step. Daily plasma exchange should be considered if resolution is not attained within 24 h of steroid therapy. Plasma exchange is more effective than plasma infusion, because antibodies or inhibitors can be removed from the recipient and ADAMTS-13 can be replaced in the donor plasma. In patients who are recalcitrant to fresh frozen plasma, the use of cryopreserved supernatant (fresh frozen plasma minus cryoprecipitate) or solvent-detergent-treated (SD) plasma may be attempted, as these plasma products are poor in large VWF multimers. Plasma exchange therapy is most effective when implemented within the first 24 h of disease and may be required for over 2 weeks. The endpoint of therapy is resolution of thrombocytopenia (attainment of a platelet counts greater than 100,000/mm^3) and no further deterioration of neurologic status. Vincristine and/or rituximab is recommended to stop antibody production in patients who are recalcitrant to plasma exchange therapy. Chronic relapsing TTP, though much less common, requires chronic plasma infusion therapy after resolution of the acute episode. Plasma infusions may be required on a monthly basis. The benefits of these therapies are considerable. The short-term risks associated with plasma exchange therapy include the need for a large-bore intravenous catheter, hypocalcemia secondary to citrate-based anticoagulation which requires calcium replacement, and hypotension requiring inotropes or vasopressors in patients with shock and secondary catheter-related infections. The long-term risks include blood-borne virus exposure.

Disseminated intravascular coagulation is a primary determinant of outcome in critically ill children.

Disseminated intravascular coagulation is a primary determinant of outcome in critically ill children. When experimental and clinical results in neonates suggested that heparin therapy did not improve outcome in DIC, it became generally accepted that the most important determinant of outcome was aggressive fluid resuscitation, restoration of normal or hyperdynamic circulation, and removal of the nidus of infection and/or systemic coagulation. The early years of pediatric intensive care has been successfully focused on this approach, such that DIC is now the least common manifestation of organ failure in children with multiple organ failure. However, despite reversal of shock, there are still children who develop DIC.

Coagulopathy is a predictor of mortality if it persists in children with multiple organ failure.

Coagulopathy is a predictor of mortality if it persists in children with multiple organ failure. The present mainstay of therapy with the thrombotic phenotype of DIC is replacement of plasma until PT/aPTT is corrected. This approach could be theoretically counterproductive in some patients. Although PT/aPTT can be improved as antithrombin III, protein C, thrombomodulin, and protein S are being replaced, concerns are raised as to whether concomitant replacement of coagulation factors in fresh frozen plasma is "fueling the fire." For this reason, many investigators who use plasma infusion recommend concomitant heparin infusion to allow ongoing anticoagulation. In countries where antithrombin III or protein C concentrates are available, physicians may use these concentrates in place of, or in combination with, plasma infusion. Both approaches have been found to be effective in reversing DIC. Some investigators theorize that activated protein C may be more effective if the ability of the host to activate this protein is diminished. However, data suggest that children with meningococcemia and adults with infectious purpura can activate exogenously administered protein C. Tissue factor pathway inhibitor concentrate is also effective in reversing DIC, but this therapy requires further investi-

gation. Several other infusion therapies have been promoted. Many use heparin to prevent ongoing thrombosis; however, heparin is a cofactor for antithrombin III and therefore does not prevent clotting efficiently if antithrombin III levels are low. Moreover, combined use of heparin and antithrombin III concentrate can cause an increased tendency to bleeding. Prostacyclin infusion can improve microcirculatory flow and decrease platelet thromboses. Other infusion therapies with similar effects include nitroglycerin, nitroprusside, milrinone, and pentoxifylline. Case reports describe fibrinolytic therapy with tPA, urokinase, or streptokinase, resulting in remarkable restoration of limb perfusion and unexpected survival in children with purpura fulminans. Continued use of urokinase requires intermittent plasma infusion to replace depleted plasminogen. The untoward complication of continued use of fibrinolytic therapies can be bleeding, if exogenous plasminogen activator activity is far greater than endogenous plasminogen activator inhibitor activity. It is likely prudent to maintain higher platelet counts and procoagulant factor levels (e.g., platelet, fresh frozen plasma [FFP] and cryoprecipitate infusion), when using fibrinolytic therapies. If patients develop life-threatening bleeding from these therapies, then antifibrinolytic therapies, including aminocaproic acid, tranexamine, and aprotinin, may be considered.

Plasma exchange is a nonspecific therapy, which has been reported to be effective for the reversal of DIC.

Plasma exchange is a nonspecific therapy, which has been reported by several groups to be effective for the reversal of DIC. These centers use whole blood exchange when infants are too small to tolerate the volume of extracorporeal blood or the large-bore catheter needed for centrifugation-based plasma exchange. The theory behind this therapy is straightforward. Plasma exchange allows for the simultaneous correction of the abnormalities of DIC, including increased circulating tissue factor and plasminogen activator inhibitor activity and decreased antithrombin III, protein C, protein S, and prostacyclin activity without incurring extreme fluid overload. Plasma exchange is performed using a one and a half volume exchange, which replaces approximately 78% of the host plasma. One series demonstrated that plasma exchange was associated with improvement in coagulopathy and survival of 7 of 8 children, with meningococcal associated purpura fulminans, who had a predicted mortality of greater than 90% based on a prolonged aPTT. An aPTT >50 s is predictive of a poor outcome in children with meningococcemia. In that report, the aPTT corrected because factor II, V, VII, and VIII levels were restored. However, protein C and antithrombin III levels were only minimally increased by plasma exchange. The attainment of a protein C level of 0.25 IU/mL is associated with normalization of coagulation in neonates with congenital purpura fulminans. The supplementation of plasma exchange with protein C and antithrombin III has the potential to be efficacious in patients with consumptive microangiopathy.

The prototype of the procoagulant form of DIC has been found in children with dengue fever (primarily in Southeast Asia). Physicians from Thailand have been credited with effective management approaches that have been associated with a tenfold reduction in mortality. Similar to observations with other thrombotic forms of DIC, the rapid reversal of shock is the most effective therapy. Children are continuously fluid resuscitated using hemoglobin as an endpoint. If hemoglobin concentrations increase, then it is indicative of hemoconcentration and hypovolemia, and more isotonic fluids are then given. This therapy is continued until the virus runs its course. There are a minority of children who develop bleeding diathesis despite adequate resuscitation. These children will exsanguinate without aggressive therapy. Unlike the practice in the Western world, hospitals that serve endemic dengue populations store whole blood rather than component blood products. These practitioners simply replace patient blood loss with whole blood whenever hemoglobin falls, providing a type of whole blood exchange therapy without the exchange

machine. The therapy is continued until the viral course is complete. This clinical approach has been associated with successful outcomes.

Anti-C5 antibody (eculizumab) is currently recommended for patients diagnosed with atypical HUS. For STEC-HUS, the benefit of eculizumab is still unclear and ongoing clinical trials will help to clarify its role. Therapeutic plasma exchange is a therapeutic strategy that can be started during the initial acute episode for which a clear diagnosis is not yet established such as pending complement, ADAMTS-13 and VWF levels. For those diagnosed with autoantibodies to complement inhibitors, such as factor H, then immune suppression to decrease antibody production with steroids, cyclophosphamide, and/or rituximab may be tried.

Secondary thrombotic microangiopathy may be diagnosed in critically ill patients with new-onset thrombocytopenia, organ failure, and elevated LDH.

Secondary thrombotic microangiopathy may be diagnosed in critically ill patients with new-onset thrombocytopenia, organ failure especially acute kidney injury, and elevated LDH or with an underlying predisposing condition (■ Table 3.2). Poor outcomes from these disease processes are well-documented. Favorable responses of adults and children with secondary thrombotic microangiopathy have been found with the use of the TTP-based plasma exchange therapy protocol. The biologic plausibility for the beneficial effects of plasma exchange in patients with TTP or DIC has been discussed, and the biologic plausibility for the therapeutic effect in patients with 2° TMA is similar. Plasma exchange normalizes plasminogen activator inhibitor-1 activity, allowing endogenous tissue plasminogen activator to lyse fibrin in a controlled and progressive fashion without bleeding. Plasma exchange also has a beneficial effect on VWF pathophysiology. It removes ADAMTS-13 inhibitors and ultra-large VWF multimers, restores ADAMTS 13 activity, and improves organ function.

Currently, there are ongoing trials of specific therapies for sepsis-induced systemic thrombosis, including trials of thrombomodulin. Unfortunately, there have been many prior failed trials, including activated protein C, tissue factor pathway inhibitor, and heparin. Current recommendations from the International Society on Thrombosis and Haemostasis are to provide supportive care with blood product replacement while performing prospective controlled trials to evaluate the benefit of specific therapies. For nonspecific therapy, two nonrandomized multicenter registry studies in children with thrombocytopenia-associated multiple organ failure showed that therapeutic plasma exchange was associated with improved survival. These multicenter registry studies followed an initial pilot study in children with thrombocytopenia-associated multiple organ failure that showed plasma exchange therapy could correct the coagulopathy, VWF-mediated thrombogenicity, and reverse organ failure. In addition, a single center study in adults with severe sepsis using plasma exchange therapy showed a reduction in mortality by 20%, which, however, was not statistically significant after adjustment for effects of unbalanced baseline characteristics.

In general, 1 mL per kg of fresh frozen plasma provides the equivalent of 1.5–2 unit/kg of procoagulant and anticoagulant activity.

Bleeding disorders can also be managed with specific and nonspecific therapies. In patients with congenital deficiencies, specific factors, such as factor VIII and factor IX, concentrates may be given for hemophilia just as protein C concentrate and antithrombin III concentrates may be given for purpura fulminans. However, plasma may also be effectively given. In general, 1 mL per kg of FFP provides the equivalent of 1.5–2 unit/kg of procoagulant and anticoagulant activity, since plasma volume is roughly 50–60 mL/kg. For most factors, a percentage activity > 30% or 15–20 mL/kg of FFP prevents proclivity to clotting (anticoagulant factors) or bleeding (procoagulant factors). However, if factors are being consumed by DIC or trauma-associated bleeding, then greater volumes of plasma will be necessary, or the use of multiple concen-

Activated factor VII can be used to stop life-threatening bleeding under some circumstances.

trates will be needed. Activated factor VII can be used to stop life-threatening bleeding under these circumstances. Plasma exchange therapy can be used to give 50–80 mL/kg of plasma (one and a half to two volume exchange) without fluid overload. In patients with fibrinolysis, the antifibrinolytics may be lifesaving (Table 3.3).

3.3 Conclusion

A consensus is developing that disseminated microvascular thrombosis and bleeding is a therapeutic target in children with thrombocytopenia-associated multiple organ failure. As with all therapeutic targets, the underlying cause of the disease must be removed for the therapy to have a long-term effect. Microvascular thrombosis and bleeding is associated with systemic insults, including shock, infection, drugs, toxins, and radiation. In order for therapies directed at microangiopathy to be beneficial, shock must be reversed, infection eradicated and removed, and precipitating drugs, toxins, and radiation stopped. Antithrombotic/fibrinolytic therapies can be expected to have the greatest effect on outcome when these tasks have been accomplished.

New-onset thrombocytopenia may be useful as an indicator of thrombotic microangiopathy in children with multiple organ failure. Although bone marrow aspirates/biopsy may diagnose bone marrow infiltration or bone marrow suppression, it has been found that many patients with infiltrative disease also have microangiopathy. Accurate diagnosis will require development of a user-friendly assay of ADAMTS-13, VWF multimeric analysis, and complement activities. For now, resolution of thrombocytopenia is a useful indicator of resolving thrombotic microangiopathy and a reasonable endpoint for successful use of antithrombotic and fibrinolytic therapies.

Randomized controlled trials suggest that steroids and nonspecific plasma exchange therapy improves survival for adult patients with primary TTP and adult patients with severe sepsis. Two nonrandomized multicenter registry studies suggest that plasma exchange therapy could correct coagulopathy, VWF-mediated thrombogenicity, and reverse organ failure in children with thrombocytopenia-associated multiple organ failure. Currently, there is no specific therapy (i.e., no monotherapy) that has been shown to improve outcome for sepsis-induced coagulopathy. Plasma infusion or exchange should be considered until normalization of PT/aPTT. Concomitant anticoagulant therapy is also recommended with low-dose heparin, antithrombin III, or protein C concentrates. The use of fibrinolytics has been recommended by some for patients with life-threatening or limb-threatening thrombosis. Careful attention to normalization of the platelet count and the PT/aPTT is recommended before therapy is initiated. Antifibrinolytics or activated factor VII can be used, if life-threatening bleeding ensues. Fresh whole blood banking procedures may have efficacy in hospitals with populations in common need of treatment for the hemorrhagic phenotype of DIC. Anti-C5 antibody (eculizumab) can be used in atypical HUS. In patients with bleeding disorders, specific and nonspecific therapies are also recommended. Specific therapies include platelets; factors VII, VIII, and IX; and antifibrinolytics, and nonspecific therapies include plasma infusion and plasma exchange.

Review Questions

1. Thrombotic thrombocytopenic purpura may be distinguished from nonconsumptive secondary thrombotic microangiopathy by the presence of:
   A. Altered mental status
   B. Fever
   C. Microangiopathic hemolysis
   D. Renal dysfunction
   E. Thrombocytopenia

2. Which of the following is the most essential component of the fibrinolytic pathway and the mediator of fibrinolysis?
   A. Activated factor VII
   B. Plasmin
   C. Protein S
   D. Thrombin
   E. von Willebrand fragment

3. Which of the following accurately describes a step in the process of forming a fibrin clot at the site of a focal traumatic vascular injury?
   A. The endothelial disruption results in the release of prostacyclin, which produces local vasoconstriction.
   B. The liver produces ultra large von Willebrand fragment (vWF) multimers, which initiate platelet aggregation and form the platelet plug at the site of endothelial disruption.
   C. The loss of endothelium at this site exposes tissue factor, which inhibits activation of factor VII.
   D. Thrombin activatable fibrinolysis inhibitor (TAFI) increases plasminogen activator inhibitor type-1 (PAI-1) activity, thereby fostering fibrinolysis.
   E. Thrombin production activates thrombin activatable fibrinolysis inhibitor (TAFI) at the site of the injury.

4. Which of the following pathophysiological mechanisms accounts for the clinical syndrome of acute thrombotic thrombocytopenic purpura (TTP)?
   A. A change in the metabolic milieu (e.g., acidosis) results in decreased ADAMTS 13 activity, leading to the inability to cleave unusually large and large von Willebrand fragment multimers to their smaller, less thrombogenic multimers.
   B. Shear injury of the vascular endothelium exposes tissue factor, resulting in the exuberant activation of factor VII, ultimately resulting in a prothrombotic state with high concentrations of unusually large and large von Willebrand fragment multimers.
   C. The formation of antibodies against the vWF-cleaving proteinase (ADAMTS 13) destroys vWF cleaving proteinase activity, resulting in the inability to cleave unusually large and large von Willebrand fragment multimers to their smaller, less thrombogenic multimers.
   D. There is a congenital deficiency of ADAMTS 13, which is exacerbated during intercurrent episodes of shear stress, resulting in the inability to cleave unusually large and large von Willebrand fragment multimers to their smaller, less thrombogenic multimers.
   E. There is an inherited predisposition to decreased protein C activity that is exacerbated by intercurrent disease processes, resulting in a prothrombotic state and high concentrations of unusually large and large von Willebrand fragment multimers.

5. A 6-year-old child who presented with fever and generalized tonic-clonic seizure activity requires intubation for airway control. His heart rate is 145 beats per minute, his blood pressure is 128/85 mm Hg, and his oxygen saturation is 100% on 30% oxygen via the ventilator. He is oliguric making approximately 0.8 mL/kg/h of urine. Laboratory analysis reveals the following:
   - Sodium: 132 mEq/L
   - Potassium: 5.4 mEq/L
   - Chloride: 95 mEq/L
   - Bicarbonate: 16 mmol/L
   - Blood urea nitrogen: 68 mg/dL
   - Creatinine: 3.2 mg/dL
   - Glucose: 232 mg/dL
   - White blood cell count: 6200/μL
   - Hemoglobin: 6.5 g/dL
   - Platelet count: 37,000/μL
   - Lactate dehydrogenase: 3326 units/L
   - Which of the following therapies would be most indicated for this child?
     A. Continuous venovenous hemofiltration
     B. Intravenous immunoglobulin
     C. Packed red blood cell transfusion
     D. Plasma exchange
     E. Platelet transfusion

6. Which of the following is activated by thrombin to reduce the production of plasmin and inhibit fibrinolysis?
   A. Activated factor VII
   B. Protein S
   C. Thrombin activatable fibrinolysis inhibitor (TAFI)
   D. Tissue plasminogen activator
   E. von Willebrand fragment

7. Which of the following is expressed by the endothelium and activates protein C, thereby ultimately promoting fibrinolysis?
   A. Plasmin
   B. Thrombin activatable fibrinolysis inhibitor (TAFI)
   C. Thrombin
   D. Thrombomodulin
   E. Tissue factor pathway inhibitor

8. Which of the following circulates throughout the vascular system forming complexes with any released tissue factor to prevent factor VII-mediated coagulation?
   A. Plasmin
   B. Plasminogen activator inhibitor type-1 (PAI-1)
   C. Protein C
   D. Tissue factor pathway inhibitor
   E. Thrombomodulin

9. The following are true about hemolytic uremic syndrome (HUS) except:
   A. HUS is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure.
   B. Involves thrombosis without endothelial injury.
   C. Commonly occurs in the United States secondary to infection with toxin-producing *E. coli.*

D. Can involve the brain, pancreas, and other organs.
E. Responds to plasma exchange for atypical forms.

10. A 12-year-old child presents with fever, rash, and weak distal pulses and cool extremities. His heart rate is 178 beats per minute, and his blood pressure is 72/35 mm Hg. Laboratory analysis reveals the following results:
- pH: 7.27
- $PaCO_2$: 27 mm Hg
- PaO_2: 94 mm Hg
- Base deficit: −15.3
- Hemoglobin: 7.5 g/dL
- White blood cell count: 1200/μL
- Platelet count: 38,000 /μL
- PT: 21 s
- aPTT: 75 s
- A blood culture is positive for gram-positive cocci in chains. In addition to the reversal of shock, the therapy most likely to improve his likelihood for a successful outcome is:

A. Appropriate antimicrobial therapy
B. Bicarbonate therapy
C. Intubation and mechanical ventilation
D. Packed red blood cell transfusion
E. Plasma exchange

11. Nonconsumptive secondary thrombotic microangiopathy may be distinguished from disseminated intravascular coagulation based on the presence of which of the following hematologic parameters?

A. Anemia
B. Increased D-dimer levels
C. Increased or normal fibrinogen levels
D. Leukocytosis
E. Thrombocytopenia

12. What is the final product of the complement pathway activation that causes destruction to the endothelium during HUS?

A. C3b
B. Terminal C5a
C. Thrombomodulin
D. Membrane attack complex
E. C5

Answers

1. C
2. B
3. E
4. C
5. D
6. C
7. D
8. D
9. B
10. A
11. C
12. D

Suggested Readings

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The Inflammatory Response

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Contents

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Learning Objectives

1. Describe the cellular components of the immune system that determine the inflammatory response.
2. Understand the roles of the innate and adaptive immune systems in initiating and regulating the inflammatory response.
3. Describe the role of cytokines and chemokines in regulating the inflammatory response.
4. Describe the role of the complement system in the inflammatory response.
5. Understand the roles of other mediators, including eicosanoids, kinins, nitric oxide, glucocorticoids, and heat-shock proteins in modulating the inflammatory response.
6. Discuss the triggering and intracellular signaling mechanisms involved in inflammation, including the toll-like receptor/NFκB, JAK/STAT, and MAP kinase pathways.
7. Describe the impact of immunomodulatory strategies aimed at the reduction of hyperinflammation.
8. Describe the phenomenon of immunoparalysis and its importance in critically ill patients.
9. Understand the role of immunostimulatory therapies in the reversal of immunoparalysis.
10. Identify HLH/MAS as an important inflammatory phenotype in critical illness.
11. Understand the impact of critical illness itself on the inflammatory response.
12. Identify the unintended immunomodulatory effects of commonly used medications in the ICU.

4.1 Introduction

The activation and migration of leukocytes during infection or injury and the associated physiologic changes that occur thereafter characterize the inflammatory response. This response represents the body's attempt to identify, contain, and eliminate pathogens and to initiate tissue repair mechanisms. If this response becomes systemic, it results in an important source of morbidity and mortality in the pediatric intensive care unit (PICU). Septic shock, for example, can be thought of as the body's deadly overreaction to microbial invasion. Mediators and mechanisms of the inflammatory response are increasingly well understood, but treatments targeting inflammation in the ICU have been historically ineffective at improving outcomes. Mounting evidence suggests that a balance between pro- and anti-inflammatory influences is crucial for recovery from critical illness. In this chapter, this balance will be explored on both intra- and extracellular levels. The discussion will then shift back to the bedside to review the history of immunomodulation in the ICU, describe the impact of intensive care on the inflammatory response, and highlight promising areas of research into the modulation of the inflammatory response.

4.2 SIRS and CARS

SIRS and CARS represent opposite extremes of the inflammatory response.

The systemic inflammatory response syndrome (SIRS) and the compensatory anti-inflammatory response syndrome (CARS) can be thought of as opposite extremes of the inflammatory response (Fig. 4.1). SIRS has been defined as a clinical state characterized by at least two of the following findings: abnormal temperature (>38 °C or <36 °C), tachycardia, tachypnea (or hyperventilation),

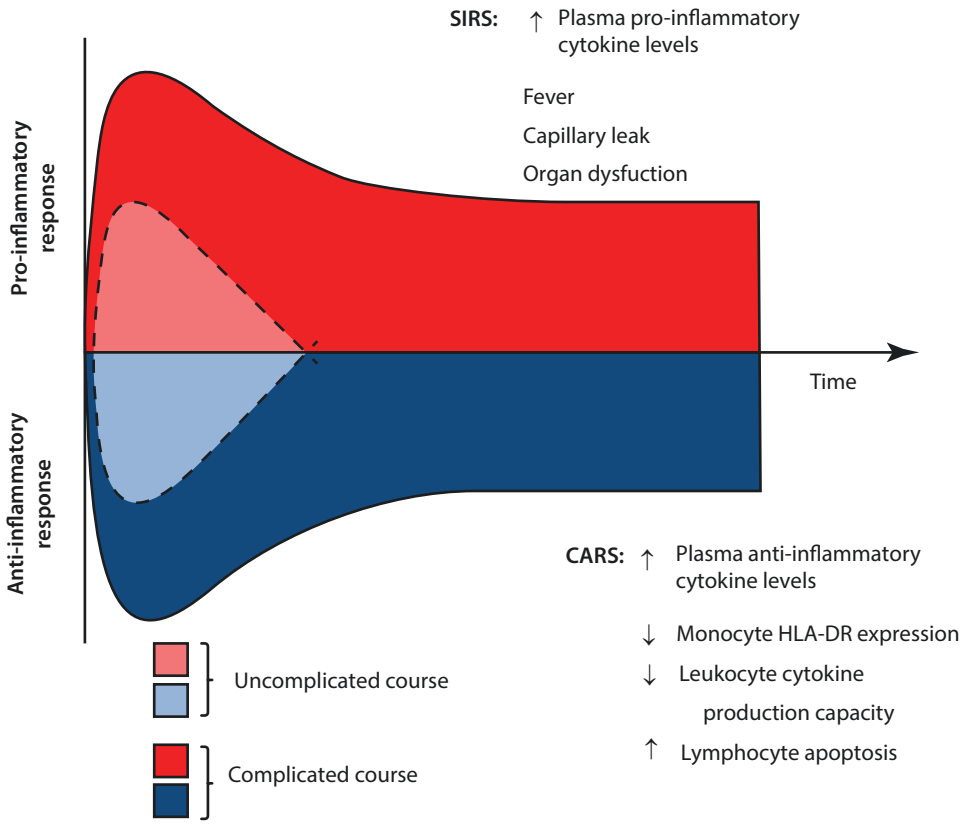

Fig. 4.1 The immunologic effects of the SIRS and CARS responses

and/or an abnormal white blood cell count (>12,000 cells/mm^3, <4000 cells/mm^3, or >10% bands. In the setting of documented or suspected infection, this syndrome has been historically known as sepsis. The inflammatory phenotype, however, is characteristic of many clinical states commonly seen in the PICU, including trauma and the post-operative state. CARS represents the body's attempt to restore homeostasis following an inflammatory insult through the near-simultaneous induction of counter-regulatory anti-inflammatory mechanisms. In contrast to SIRS, with its clinically obvious signs and symptoms, including fever, hemodynamic changes, and evidence of tissue malperfusion, CARS is typically asymptomatic. CARS, when severe and persistent, represents a form of acquired immunodeficiency and is itself associated with morbidity and mortality. The balance between pro- and anti-inflammatory influences is therefore key in determining the overall immune response.

4.3 Leukocytes and Inflammation

The cellular elements of the immune system can be divided into two main groups, those of the innate and adaptive immune systems. Both are required for a fully competent immune response, but they function in very different ways. The cells of the innate immune system (e.g., monocytes, macrophages, dendritic cells, natural killer (NK) cells, neutrophils) can recognize and respond to large subgroups of pathogens based on constitutively expressed pattern recognition receptors. For example, all monocytes respond to lipopolysaccharide (LPS) through its binding to the CD14/TLR4 complex. Innate immune cells do not require specific processing and presentation of antigens in order to become activated. They are themselves active in antigen processing and presentation to

cells of the adaptive immune system (discussed below). Under normal circumstances, innate immune cells display a similar immune response each time they encounter a given stimulus, rather than exhibiting an augmented or memory response with repeated exposures.

The innate immune system responds to the general classes of pathogens, while the adaptive immune system provides a highly antigen-specific immune response.

By contrast, the cells of the adaptive immune system (lymphocytes) become activated via the binding of highly specific receptors (surface immunoglobulin for B cells; the T cell receptor for T cells), whose specificity is the result of gene rearrangement within each individual cell. This allows for a high degree of lymphocyte diversity within a given individual. A repertoire of more than 1×10^{11} discreet antigens can be recognized by the adaptive immune system as a result of these rearrangements. Cells of the adaptive immune system usually require help, in the form of antigen presentation, from the innate immune cells to produce an effective immune response. This process starts with the ligation of the T cell receptor by an antigen-bearing class II major histocompatibility complex (MHC) molecule such as human leukocyte antigen (HLA)-DR on an innate immune cell. For activation to occur, a simultaneous co-stimulatory interaction must also occur between receptors on the T cell (e.g., CD28) and ligands on the antigen-presenting cell (APC) (e.g., CD80, CD86). Inhibition of the lymphocyte response can occur if co-inhibitory molecules are ligated instead (e.g., PD-1 [lymphocyte] and PD-L1 [APC]). Similarly, B cells often require co-stimulation by antigen-specific T cells to optimize antibody production. Lastly, the T and B cell populations, once activated, are both capable of producing memory cells that can respond more promptly and more robustly to repeated exposure to an antigen. The innate immune system, by virtue of its pattern recognition receptors, is typically the first cellular group to become activated by a given stimulus (over minutes to hours). The adaptive immune response usually requires more time for antigen processing, activation, proliferation, and differentiation (hours to days), leading to clonal expansion (several days). The following section will focus on how both arms of the immune system have highly specific roles but are ultimately complementary in maintaining and modulating the inflammatory response.

4.4 Innate Immunity

4.4.1 Pathogen Recognition

The effector cells of the innate immune system include neutrophils, monocytes, macrophages, dendritic cells, and NK cells.

Innate immune cells recognize pathogen-associated and damage-associated molecular patterns through receptors, including the toll-like receptors.

The major effector cells of the innate immune system include monocytes (which mature into macrophages upon activation and migration out of the bloodstream), neutrophils or polymorphonuclear cells (PMN), dendritic cells, and natural killer (NK) cells. Their properties are summarized in ◘ Table 4.1. As a group, these immune effector cells serve to ingest pathogens and effect intracellular killing, process and present antigens to adaptive immune cells, and produce chemicals that attract other lymphocytes to the area (chemokines) or directly induce inflammatory effects (cytokines). Most innate immune cells express cell-surface and intracellular receptors, which recognize and are activated by broad classes of molecules deemed PAMPs (pathogen-associated molecular patterns) and DAMPS (damage-associated molecular patterns) (see ◘ Table 4.2). Toll-like receptors (TLRs) are among the best characterized cell-surface receptors that interact with PAMPs. These receptors bind to families of ligands and initiate intracellular signaling cascades culminating in the activation of nuclear factor-κB (NFκB) and the transcription of pro-inflammatory gene products (see ▶ Sect. 4.7). In addition to TLRs, macrophages also express mannose receptors that result in phagocytosis of pathogens bound to their cell

Table 4.1 Cellular components of the innate immune system

Cell type	Site	Pathogen triggers	Receptor	Cytokine triggers	Primary actions	Mediators produced upon activation
PMN	Blood/ tissue	Bacterial peptides, opsonization	Chemotactic receptors, FcR	IL-8, FcR binding	Phagocytosis, intracellular killing, antigen presentation	TNFα, IL-1ra, ROS, BPI, lytic enzymes
Monocyte	Blood	TLR ligands, opsonization	Toll-like receptors, CD14, FcR	IFNγ, GM-CSF, TNFα, IL-1-β, IL-19, MIF	Antigen presentation, phagocytosis, cytokine/chemokine production	TNFα, IL-1β, IL-6, IL-8, IL-10, IL-19, IL-20, IL-27, TGFβ, IL-1ra
Macrophage	Tissue	TLR ligands, mannose, acetylated lipoproteins, opsonization	TLRs, CD14, mannose receptor, scavenger receptor. FcR	IFNγ, GM-CSF TNFα, IL-1-β, MIF	Antigen presentation, phagocytosis, intracellular killing, cytokine/ chemokine production	TNFα, IL-1β, IL-6, IL-8, IL-10, IL-12, IL-18, IL-27, IL1ra
Dendritic cell	Tissue/ lymph	TLR ligands, opsonization	TLRs, FcR	Flt3L, GM-CSF	Antigen presentation	IFNα, IL-12, IL-23, IL-27
NK cell	Blood/ tissue	Absence of MHC class I	Lectins	IL-12, IL-15, IL-18	Lysis of target cell	TNFα, IL-22, MIP-1α, perforin, granzymes

BPI bactericidal/permeability-increasing protein, *FcR* Fc receptor, *Flt3L* Flt3 ligand, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *IFN* interferon, *IL* interleukin, *IL-1ra* interleukin-1 receptor antagonist, *MHC* major histocompatibility complex, *MIF* macrophage migration inhibitory factor, *MIP* macrophage inflammatory protein, *NK* natural killer, *PMN* polymorphonuclear cell, *ROS* reactive oxygen species, *TGF* transforming growth factor, *TLR* toll-like receptor, *TNF* tumor necrosis factor

Table 4.2 Pattern recognition receptors of innate immune cells

Receptor	Ligands	Ligand sources
TLR1	Triacyl lipopeptides	Bacteria and mycobacteria
TLR2	Peptidoglycans Lipoteichoic acid Lipoproteins Zymosan HMGB-1	Gram-positive bacteria Bacteria Fungi Damaged host cells
TLR3	Double-stranded RNA	Viruses
TLR4	Lipopolysaccharide HMGB-1	Gram-negative bacteria Damaged host cells
TLR5	Flagellin	Bacteria
TLR6	Lipoteichoic acid Zymosan	Gram-positive bacteria Fungi
TLR7	Single-stranded RNA	Viruses
TLR8	Single-stranded RNA	Viruses
TLR9	Unmethylated CpG DNA Host DNA HMGB-1	Bacteria and viruses Damaged host cells Damaged host cells
TLR 11	Profilin-like protein	*Toxoplasma gondii*
Mannose receptor	Mannose	Bacteria and viruses
Fc-receptor	Fc portion of immunoglobulin	Opsonized pathogen
NOD1[a]	Diaminopimelic acid	Gram-negative bacteria
NOD2[a]	Muramyl dipeptide	Gram-positive and gram-negative bacteria

TLR toll-like receptor, *NOD* nucleotide-binding oligomerization domain
[a]Intracellular inflammasome component

surface through recognition of bacterial, fungal, or viral surface carbohydrates. Receptors which bind the Fc portion of immunoglobulin are also present on most innate immune cells. These Fc receptors allow for the identification and phagocytosis of pathogens, which have been coated (opsonized) by antibody, thus marking them for destruction.

4.4.2 Migration

Cells of the innate immune system can be activated and recruited into the periphery through interaction with adhesion molecules as well as through response to cytokines and chemokines. As a result of local damage, immune cells and vascular endothelial cells upregulate expression of proteins on their surfaces that result in the adhesion of leukocytes to the vascular lining and ultimately their migration through it to become tissue effector cells. The groups of proteins most important in these interactions are the selectins and intercellular adhesion molecules (ICAM), expressed by endothelium, and the integrins and chemokine receptors, expressed by leukocytes. The classic example of this

process is the rolling of neutrophils across the vascular endothelial surface mediated by binding of endothelial E-selectin to the Sialyl-Lewis^x antigen on the PMN. This is followed by tight binding between endothelial ICAM-1 and the PMN integrin LFA-1. Migration into the tissues then occurs along a chemokine gradient (in this case IL-8).

Adhesion molecules expressed on both leukocytes and endothelial cells facilitate migration of immune cells into the tissues.

4.4.3 Antigen Presentation

Processed antigens are displayed by most innate immune cells on MHC class II molecules including HLA-DR.

The role of innate immune cells (chiefly macrophages and dendritic cells) in antigen presentation represents a critical convergence point between the innate and adaptive immune systems. After a phagocyte recognizes a pathogen through PAMP receptors or as the result of opsonization, the pathogen is engulfed and undergoes degradation in the phagolysosome. The resultant small peptides are then loaded onto MHC class II molecules including HLA-DR. These HLA-DR molecules carrying foreign peptides are then transported back to the cell surface, where they are displayed and ultimately presented to T cells, contributing to activation of the adaptive immune response. As an example of the importance of this process, reduction in HLA-DR expression on circulating monocytes has been associated with adverse outcomes in the setting of adult and pediatric critical illness (see ► Sect. 4.9).

4.4.4 NK Cells

NK cells are the only cells of lymphoid origin to be included in this review of the innate immune system (While B lymphocytes do express Fc receptors and can present antigen, the highly cell-specific nature of the surface immunoglobulin-ligand relationship places them in the adaptive immune system for the purposes of this discussion). NK cells express cell-surface lectin-like proteins that bind carbohydrates on host (self) cells. Ligation of these receptors induces the release of granules containing perforin and granzymes. These proteins result in cell membrane damage and apoptosis of the target cell. This process is inhibited by simultaneous ligation of host cell MHC class I molecules by the NK cell's killer cell immunoglobulin-like receptors (KIRs). Thus, only host cells whose MHC class I molecules have been destroyed or mutated by viral infection or malignancy are subject to destruction by NK cells. In addition to cytotoxicity toward virally infected host cells and those which have undergone malignant transformation, NK cells may play a significant role in airway inflammation. NK cells also play an important part in the compensatory anti-inflammatory response through their role in killing activated immune cells. Congenital or acquired reduction in NK cell activity is central to the pathogenesis of primary and secondary hemophagocytic lymphohistiocytosis (HLH).

4.5 Adaptive Immunity

While the innate immune system is crucial for the initiation and propagation of the inflammatory response, the adaptive immune system contributes to the persistence and modulation of that response. Antibodies produced by mature B cells (plasma cells) serve as activators of the innate immune cells via Fc receptors. Similarly, certain T cells produce cytokines that activate innate effector cells. Other T cells produce anti-inflammatory cytokines, which downregulate the inflammatory response.

T cell precursors undergo both positive and negative selection in the thymus in order to limit self-reactivity. During this process, T cells also differentiate into CD4 or CD8 positive cells. CD8+ T cells are cytotoxic cells that release lytic granules upon contact with a pathogen or pathogen-infected cell. Also, key to the inflammatory response are CD4+, or helper, T cells. A naïve CD4+ T cell, once activated, proliferates and differentiates into one of several subtypes, depending on the local cytokine milieu at the time of activation. While numerous subtypes of CD4+ T cells have been characterized, the T-helper 1 (T_H1) and T-helper 2 (T_H2) lymphocytes are of particular relevance to the immune response in critical illness. T_H1 cells activate phagocytes through the production of granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-γ (IFNγ), and other pro-inflammatory mediators. They also induce the production of opsonizing antibodies by B cells (IgG1, IgG3). T_H2 cells, on the other hand, produce cytokines such as interleukin-10 (IL-10), transforming growth factor-β (TGFβ), and other mediators, which promote an anti-inflammatory phenotype. T_H2 cells are also more potent activators of B cells, leading to enhanced production of neutralizing antibodies (IgM), and are active in hypersensitivity and autoimmune responses. The balance between the T_H1 and T_H2 phenotypes therefore serves as an important regulatory mechanism for the inflammatory response.

Other classes of CD4+ T cells have been shown to be important in modulating the immune response. Regulatory T cells (T_{reg}) are known to be potently immunosuppressive through cell contact-mediated inhibition as well as robust production of anti-inflammatory cytokines, such as IL-10 and TGFβ. Regulatory T cells can be identified by their cell-surface marker expression pattern (CD4+ CD25+ $CD127^{lo}$) and presence of the transcription factor Foxp3. On the other end of the inflammatory spectrum, high IL-17-producing T_H17 cells are potently pro-inflammatory and have been implicated in human allergic and inflammatory disease.

NK cells induce lysis of target cells that do not express compatible MHC class I molecules.

Newly activated T cells can differentiate into T_H1 cells, which mediate a pro-inflammatory response, or T_H2 cells, which can mediate an anti-inflammatory response.

4.6 Circulating Mediators of Inflammation

4.6.1 Cytokines

While leukocytes exert their effects in part by direct cellular action (phagocytosis, intracellular killing, cytotoxicity), the clinical syndrome of SIRS is largely the result of circulating proteins released by leukocytes, vascular endothelium, and other parenchymal cells upon activation by an inflammatory stimulus. These mediators are termed chemokines, if their primary action is to recruit other immune effector cells to the area, or cytokines, if their primary action is to modulate the function of a target cell in some way. Cytokines can exert pro-inflammatory or anti-inflammatory effects, depending upon which receptors and intracellular signaling pathways are activated. The production, action, and regulation of cytokines and chemokines are exceedingly complicated processes involving multiple cell types and feedback mechanisms. For the purposes of this chapter, an overview of a limited set of cytokines, their producers, targets, signaling mechanisms, and actions is provided in Table 4.3.

In brief, IL-1β, TNFα, IFNγ, IL-17, IL-18, IL-2, MIF, and GM-CSF are examples of mediators of the pro-inflammatory (T_H1-like) response. In contrast, IL-10, TGFβ, IL-13, IL-5, and IL-4 are mediators of the anti-inflammatory/autoimmune (T_H2-like) response. Interleukin-6 is produced by immune and endothelial cells in response to inflammatory stimuli and is the cytokine whose plasma elevations are most highly correlated with adverse clin-

Table 4.3 Overview of cytokines relevant to the inflammatory response

	Cytokine	Primary producer(s)	Primary target(s)	Primary signaling pathway(s)	Action(s)
Pro-inflammatory	IL-1β	Monocytes, macrophages	Vascular endothelium, monocyte, macrophages, T lymphocytes	NFκB	Fever, vasodilation, T cell, monocyte, macrophage activation
	TNFα	Monocytes, macrophages, T lymphocytes (T_H1), NK cells	Vascular endothelium, monocyte, macrophages, T lymphocytes	MAPK, NFκB, caspases	Fever, vasodilation, endothelial activation, apoptosis
	IL-18	Macrophages	NK cells, T lymphocytes	NFκB	T cell and monocyte activation, promotes T_H1 skewing
	IL-12	Macrophages, DCs	NK cells, T lymphocytes	JAK2/Tyk2/STAT4	Activates NK cells, promotes T_H1 skewing
	IFNγ	T lymphocytes (T_H1), NK cells	Monocytes, macrophages, T and B lymphocytes	JAK2/JAK1/STAT1	Activates monocytes and macrophages, promotes T_H1 skewing
	GM-CSF	T lymphocytes, macrophages	Monocytes, macrophages, PMN, DC	JAK2 /STAT5; NFκB	Promotes growth and activation of monocytes, macrophages, PMNs, DCs
	MIF	T lymphocytes (T_H1)	Macrophages	MAPK, PLA_2	Promotes macrophage activation, inhibits macrophage migration
	IL-6	Monocytes, macrophages, Vascular endothelium	Hepatocytes, T and B lymphocytes	JAK1/STAT1; JAK1/STAT3; MAPK	Promotes acute phase response, promotes T_H2 skewing, activates adrenal axis
Anti-inflammatory	IL-10	Monocytes, macrophages, T lymphocytes (T_H2)	Monocytes, macrophages	JAK1/Tyk2/STAT3	Inhibits monocyte, macrophage activation, promotes T_H2 skewing
	TGFβ	Monocytes, T lymphocytes (T_H2)	Monocytes, macrophages, B lymphocytes	Smad/Smad4	Inhibits monocyte, macrophage activation, promotes T_H2 skewing
	IL-13	T lymphocytes (T_H2)	T and B lymphocytes, monocytes, macrophages	JAK1/JAK3/STAT6	Inhibits monocyte, macrophage activation, promotes T_H2 skewing
	IL-4	T lymphocytes (T_H2)	T and B lymphocytes	JAK1/JAK3/STAT6	Induces lymphocyte T_H2 phenotype
	IL-1 ra	Hepatocytes, monocytes, macrophages, PMNs	IL-1 receptors	Receptor binding without activation	Prevents IL-1 action

JAK Janus-associated kinase, *MAPK* mitogen-activated protein kinase, *NFκB* nuclear factor-κB, *PLA* phospholipase A, *STAT* signal transducers and activators of transcription

ical outcomes in the setting of pro-inflammatory insults. Interleukin-6 has anti-inflammatory properties as well, including activation of the cortisol axis and promotion of a T_H2-like T cell response. For the purposes of this review, IL-6 is grouped with pro-inflammatory cytokines as elevation in its plasma concentration is usually associated with elevated levels of TNFα and IL-1β.

4.6.2 Chemokines

Chemokines can be produced by a wide variety of cell types, including immune cells. While some chemokines may serve to enhance cell activation, their main action is to induce recruitment of immune cells to target areas through migration along a concentration gradient. Chemokine proteins are traditionally grouped according to their amino acid sequences, specifically the arrangement of their cysteine (C) residues near the amino terminus. The major groups of chemokines include the CC, CXC, XC, and CX3C families (though most are of the CC or CXC varieties). The CXCL group, for example, is characterized by proteins containing an amino acid, which is flanked by two cysteines, with the letter L indicating that the protein is a ligand rather than a receptor. Conversely, the receptors for these proteins on target cells are referred to by the prefix of the chemokine followed by the letter R (e.g., CXCR1). Notable exceptions to this nomenclature include IL-8, which is the primary chemokine for neutrophils, and RANTES, an important chemokine for macrophage, PMN, NK cell, and eosinophil migration. Normal chemokine production is crucial for recruitment and activation of both innate and adaptive immune cells. Because these chemical signals are released in the context of inflammation, their plasma concentrations (particularly that of IL-8) have been linked to adverse outcomes in critical illness, including the acute respiratory distress syndrome, trauma, and sepsis.

Pro-inflammatory cytokines include IL-1β, TNFα, IFNγ, IL-2, and others. Anti-inflammatory cytokines include IL-10 and TGFβ.

Elevated systemic levels of IL-6 are associated with pro-inflammatory states, but it has both pro- and anti-inflammatory properties.

4.6.3 The Complement System

Not all innate immune effector molecules originate from leukocytes. A group of proteins manufactured in the liver and known collectively as the complement system is of great importance in the identification, clearance, and killing of pathogens. Most of these proteins are synthesized as precursor proteins, or zymogens, which require proteolytic cleavage for activation. The larger proteolytic byproducts are designated by the letter "b," while the smaller byproducts are designated by the letter "a." Through a series of self-amplifying cascades, the complement proteins ultimately serve three important functions: opsonization (marking pathogens or cells for ingestion by phagocytes), lysis of pathogens through the formation of lethal transmembrane pores, and the direct mediation of inflammation through chemokine/cytokine-like effects.

The complement system can be activated through either the *classical, alternative, or mannose-binding lectin (MBL) pathways* (see ◘ Fig. 4.2). The *classical pathway* is characterized by the binding of the C1 proteins to antigen-antibody complexes, certain bacterial cell membrane constituents, C-reactive protein, and a variety of other pathogen-associated ligands. This binding results in the recruitment and activation of C4 and C2 proteins, whose C4b and C2b byproducts combine to serve as a convertase for C3. C3 convertase activity is the convergence point for the three pathways of complement activation.

Chemokines induce migration of immune cells to target areas. Elevations in their plasma concentrations have been associated with adverse outcomes in critically ill patients.

The classical, alternative, and MBL pathways all result in the activation of C3.

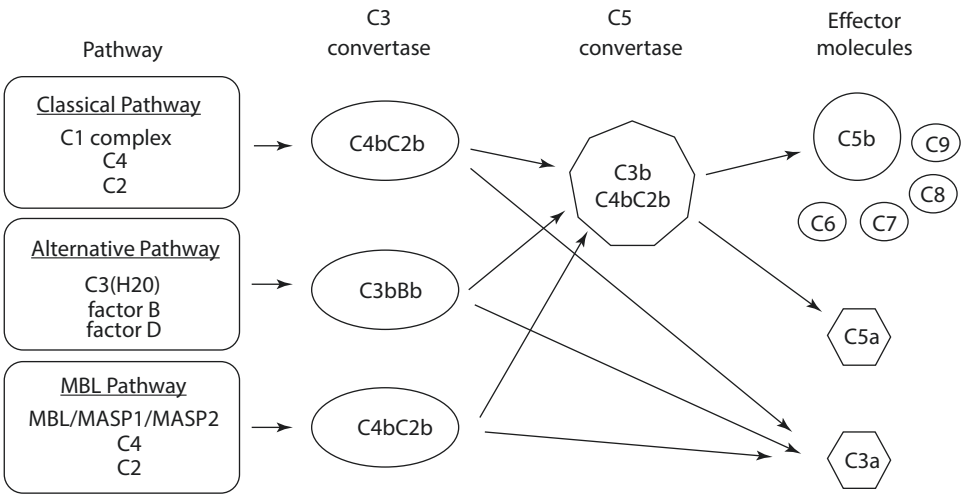

Fig. 4.2 Schematic of the complement system

The *alternative pathway* is different from the classical pathway in that it relies heavily on host (self) regulation to prevent damage to host tissues. This pathway begins with the spontaneous hydrolysis of plasma C3 (a process that is distinct from its cleavage into C3a and C3b). Hydrolyzed C3 and the plasma protein factor B form a circulating C3 convertase. The C3b produced by this $C3(H_2O)Bb$ complex can then bind to a cell surface (host or pathogen), where it can then be joined to another factor B molecule. This new membrane-bound C3bBb complex has potent C3 convertase activity. Host cells express cell-surface proteins, including complement receptor 1 (CR1), membrane cofactor protein (MCP), and decay accelerating factor (DAF), that destroy the C3bBb complex before damage can be done. Pathogens typically do not express these regulatory proteins, so C3 conversion can proceed unabated. Another plasma protein named properdin (or factor P), which binds poorly to mammalian cells but binds to many bacterial cell-surface constituents, serves to stabilize the C3bBb complex. The alternative pathway is therefore constitutively activated but is controlled by the host through negative regulation.

The last pathway of complement activation is the mannose-binding lectin pathway. MBL is a member of the family of plasma proteins known as collectins. These proteins, along with another group known as ficolins, bind to certain carbohydrate residues, including mannose, which are typically present on pathogen cell surfaces. In vertebrates, these residues have become obscured through the addition of sialic acid and other sugar groups, rendering them invisible to the MBL pathway. Once bound to an appropriate carbohydrate residue, this activated complex is now capable of activating C4 and C2 in the same manner as the C1 complex of the classical pathway. This, too, results in the formation of the C4bC2b convertase, which is capable of activating C3.

It is the cleavage of C3 into C3b and C3a which can be thought of as the first effector step in the complement system. C3a is a weakly inflammatory cytokine and chemokine. C3b, however, is the chief opsonizing molecule of the complement system. Most cells of the innate immune system express receptors for C3b that induce phagocytosis when ligated. Additionally, C3b can bind to its own C4bC2b convertase complex to form a new C5 convertase complex. C5a (known, along with C3a, as an anaphylatoxin) is a potent inflammatory cytokine, resulting in increased vascular permeability, increased endothelial adhesion molecule expression, and phagocyte recruitment. Both C3a and C5a are also thought to enhance T and B cell function through both direct and indirect mechanisms. C5b triggers the assembly of the membrane-attack com-

plex (MAC), characterized by the association of C5b, C6, C7, C8, and C9 on the pathogen cell surface. This complex forms a transmembrane pore which, if present in sufficient numbers, results in death of the pathogen.

This potentially lethal cascade of immune effector proteins has regulatory mechanisms in place to prevent inappropriate activation. The most obvious of these mechanisms is the fact that most of the proteins are present as inactive zymogens, requiring proteolytic cleavage for activation. The alternative pathway is also held in check by the presence of inhibitory host cell-surface proteins, including CR1, MCP, and DAF. In addition, the circulating plasma proteins, factor I, factor H, and C4-binding protein, disrupt the C3 convertase. These circulating regulators serve to limit the effects of the complement system to the surface of the cell which has been targeted for destruction. Another protective mechanism is the host cell-surface protein CD59 (protectin), which inhibits the formation of the membrane-attack complex on host cells.

Proteins of the complement system serve as important components of the innate immune system as well as activators of the adaptive immune response through the initiation of antigen phagocytosis for presentation and through their influence on the T and B cell responses. Complement production by the liver is constitutive but is upregulated by IL-6 in the setting of inflammation during the acute phase response. Congenital abnormalities in the complement proteins' structure or function result in clinically evident immunodeficiency with increased susceptibility to infection with *Neisseria* species.

4.6.4 The Acute Phase Response

The effector products of the complement system serve as opsonizers, cytokines, and direct mediators of pathogen killing.

The liver, when stimulated by certain cytokines, most notably IL-6, produces a number of proteins which are important for facilitating the inflammatory response, including fibrinogen, complement, C-reactive protein (CRP), serum amyloid protein (SAP), mannose-binding lectin and other collectins. CRP and SAP are multimeric molecules, which bind to bacterial and fungal cell wall constituents. There they serve as opsonizers as well as activators of the complement cascade through their interaction with the C1 complex. Serum CRP levels have historically been used as an indirect measure of inflammation, but it should be remembered that CRP is an important effector molecule of the innate immune system.

The hepatic acute phase proteins, including CRP, serve as indirect measures of inflammation as well as direct immune effector molecules.

4.6.5 Other Pro-inflammatory Mediators

In addition to the aforementioned cytokines, chemokines, and complement, there are several other classes of molecules that participate in the inflammatory response, including the eicosanoids, kinins, and nitric oxide. Eicosanoids are a group of lipid molecules, including the prostaglandins (PG), thromboxane (TX), and leukotrienes (LT), which are produced by a variety of cell types in response to stressors. Generation of these molecules requires the conversion of membrane lipid to arachidonic acid via the action of phospholipase A2. Arachidonic acid is then converted to PGH_2 by either cyclooxygenase (COX)-1 or COX-2, the targets of nonsteroidal anti-inflammatory drugs (NSAIDs). A series of constitutive and inducible synthases then generate a host of downstream effector molecules, including PGE_2 (an inhibitor of innate immune and T_H1 responses) and TXA_2 (a potent vasoconstrictor, promoter of platelet aggregation, and enhancer of innate immune and T_H1 responses). The net effect of COX-1/2 inhibition is anti-inflammatory, through reduction in TXA_2

production. Arachidonic acid can also be metabolized by the enzyme 5-lipoxygenase to produce LTA_4, which can be further modified to produce pro-inflammatory mediators, including LTB_4, LTD_4, and LTE_4. As a group, these molecules act as growth factors for innate immune cells and activators of phagocytosis and intracellular killing in phagocytes.

The kinin-kallikrein system is another family of peptides, produced by injured vascular endothelium, which serve to promote an inflammatory response. Through a cascade of zymogen activation, bradykinin and related kinins produce vasodilation, increased vascular permeability, and pain.

Arachidonic acid metabolites including TXA_2 and LTB_4 promote the inflammatory response.

Lastly, nitric oxide (NO) is produced by PMNs, monocytes, macrophages, and endothelial cells, as the result of upregulation of inducible nitric oxide synthase (iNOS) during activation by pro-inflammatory stimuli. Nitric oxide production is critical for intracellular killing by phagocytes through generation of reactive oxygen species (ROS), such as O_2^-, H_2O_2, and $ONOO^-$. Outside the phagocyte, NO results in local vasodilation and increased pro-inflammatory cytokine production and causes direct ROS-mediated oxidative tissue damage. Interestingly, NO has anti-inflammatory properties as well, including down-regulation of cellular adhesion molecules.

Nitric oxide production is critical for innate immune cells to effect intracellular killing.

4.6.6 Glucocorticoids

Glucocorticoids (GC), both endogenous and synthetic, have anti-inflammatory properties and have long been used in the treatment of inflammatory disorders. GC exert their effects through binding to the glucocorticoid receptor (GR), which is then internalized. The GC/GR complex is transported to the nucleus, where it inhibits the production of pro-inflammatory cytokines through the binding and inactivation of the pro-inflammatory transcription factor NFκB. In addition, the GC/GR complex binds to DNA and directly induces the transcription of inhibitors of inflammation including IκBα (see below). This anti-inflammatory effect seems to be highly dose dependent, however, as low doses of cortisol have been shown to enhance the hepatic acute phase response, increase expression of pro-inflammatory cytokine receptors, and increase production of macrophage migration inhibitor factor. In doses which are pharmacologically relevant to critically ill children, however, the net glucocorticoid effect is anti-inflammatory.

Glucocorticoids, in doses typically used in the ICU, result in an anti-inflammatory effect through inhibition of the NFκB pathway.

4.6.7 Heat-Shock Proteins

Heat-shock proteins (HSP) are produced by both prokaryotes and eukaryotes in response to cellular stress. Though initially discovered in the context of hyperthermic stress, these proteins are upregulated in response to a variety of stimuli, including ischemia-reperfusion and endotoxin exposure. The effect of HSP on the inflammatory response seems to be highly time dependent. If the heat-shock response is induced prior to exposure to a pro-inflammatory stimulus, cells demonstrate reduced production of pro-inflammatory cytokines. This is thought to be the result of inhibition of NFκB signaling through upregulation and enhanced function of the inhibitor IκBα (see below). If, on the other hand, the heat-shock response is induced *after* the onset of an inflammatory stimulus, it results in a pronounced apoptotic response.

Time-dependent effects of the heat-shock response include inhibition of the NKκB pathway and induction of apoptosis.

4.7 Intracellular Signaling

Mediators of inflammation, whether they are cytokines, chemokines, PAMPs, or DAMPs, can only produce their effects if the target cell is able to sense their presence, transmit that signal through the intracellular compartment, and induce the production of specific gene products. These processes are complicated, often with overlapping signaling pathways and feedback loops being activated following receptor binding by a given ligand.

4.7.1 Toll-Like Receptors and the NFκB Pathway

The TLR4/CD14 complex is the innate immune receptor for endotoxin and signals through the NFκB pathway.

NFκB must be liberated from its inhibitory molecule IκBα before it can be transported to the nucleus to serve as a transcription factor for pro-inflammatory cytokines.

As described in the innate immunity section, monocytes, macrophages, and dendritic cells possess cell-surface receptors that can recognize broad classes of pathogen-associated molecules. The TLR family is an example of these receptors, and TLR4, which is activated by bacterial endotoxin, represents a good case study of TLR signaling. LPS, bound to the plasma protein lipopolysaccharide-binding protein (LBP), binds to the cell-surface molecule CD14. LPS-bound CD14 then associates with TLR4 and its accessory proteins (see Fig. 4.3b). Successful formation of this complex leads to a series of intracellular events, including the phosphorylation of intermediary proteins. This cascade culminates in the liberation of the inhibitory protein IκBα from the transcription factor NFκB, which is then transported to the nucleus where it initiates transcription of genes encoding pro-inflammatory mediators. Multiple mechanisms of negative regulation of NFκB signaling exist. These include upregulation of IκBα mRNA production and stability, inhibition of NFκB DNA binding, and alterations in NFκB subunit arrangement such that the protein lacks a nuclear localization sequence.

4.7.2 JAK/STAT Signaling

Another important intracellular signaling pathway in the regulation of the inflammatory response is mediated by the families of proteins known as Janus-associated kinases (JAK) and signal transducers and activators of transcription (STAT). This pathway is used by a wide array of both pro- and anti-inflammatory cytokine receptors, including those for IFNγ and IL-6 (see Table 4.3). The resulting gene products depend on which STAT protein homodimer acts as the transcription factor for a given receptor. For example, when IFNγ binds to its receptor complex, it results in the phosphorylation of JAK2 and JAK1 (see Fig. 4.3a). Activated JAK1 then phosphorylates STAT1, which in turn forms a homodimer and is transported to the nucleus, where it serves as a transcription factor for pro-inflammatory genes. Multiple STAT proteins can be activated by the same JAK proteins. For example, ligation of the IL-6 receptor leads to the activation of JAK1, which can activate STAT1 (mostly pro-inflammatory gene products) and STAT3 (mostly anti-inflammatory gene products). The overall effect of ligand binding, therefore, depends on the balance between intracellular signaling pathways.

Negative regulation of the JAK/STAT pathway occurs primarily through the induction of suppressor of cytokine signaling (SOCS) proteins and phosphatases.

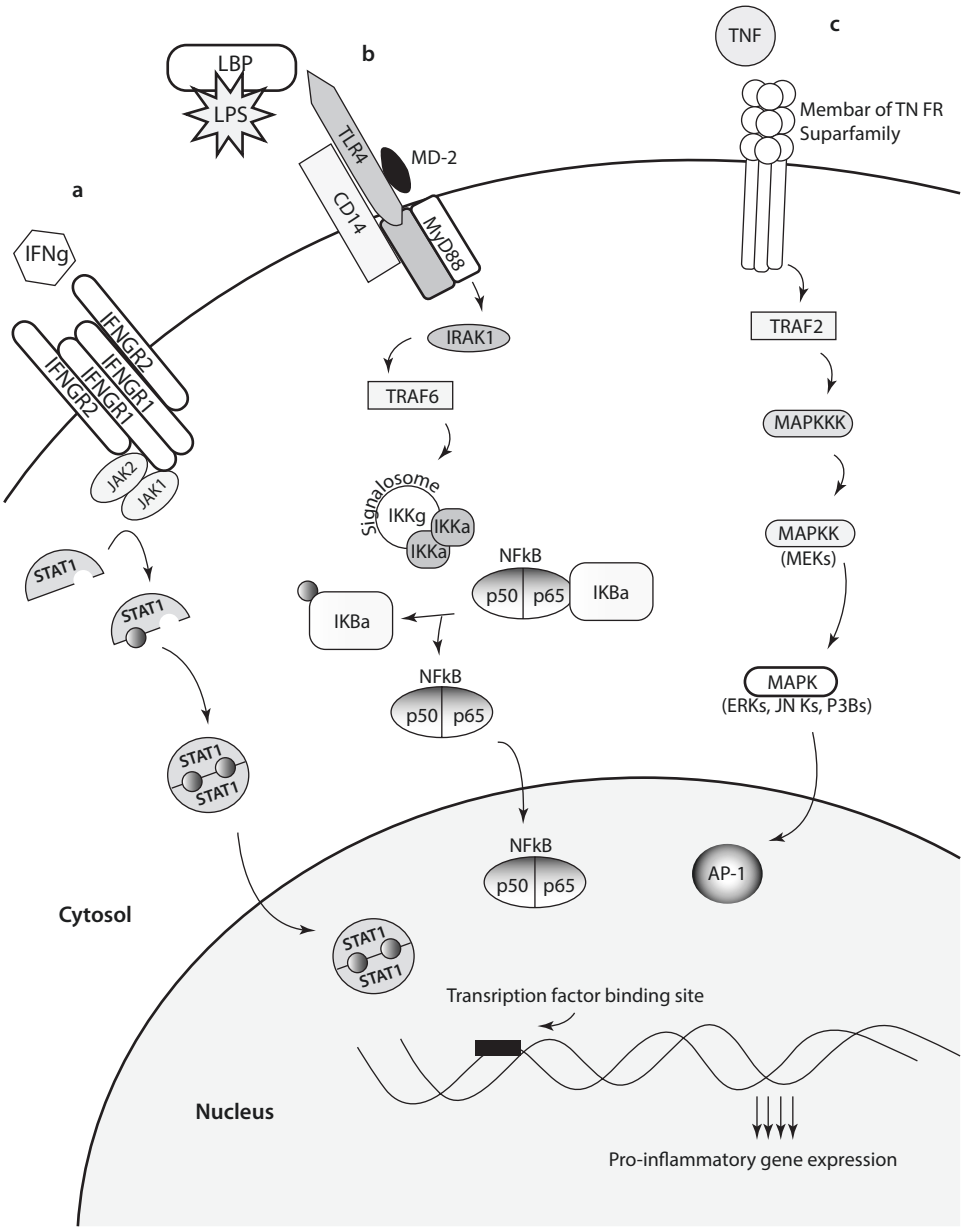

Fig. 4.3 Overview of signaling for the JAK/STAT **a**, TLR-NFκB **b**, and MAP kinase **c** pathways

The STAT family of transcription factors includes those that mediate both pro- and anti-inflammatory gene transcription.

The MAP kinases mediate pro-inflammatory gene transcription via activation of the transcription factor AP-1.

4.7.3 MAP Kinase Signaling

The mitogen-activated protein kinases (MAPK) participate in a variety of cellular processes, including growth, differentiation, and apoptosis, but they also function as signaling molecules for a number of cytokines and most chemokines. The MAP kinases extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 have all been shown to mediate pro-inflammatory gene expression and/or immune cell activation. The MAP kinases require activation from a series of upstream kinases and, ultimately, activate one of the subunits of the AP-1 transcription factor (see Fig. 4.3c). The MAPK system is negatively regulated by the action of MAPK phosphatases (e.g., MKP1), which prevent transcription factor activation.

4.7.4 G-Protein-Mediated Signaling

Activation of receptor, which result in cell migration (e.g., chemokine receptors) or phagocytosis (e.g., Fc receptors), typically results in the activation of G-proteins, which signal through phospholipase C (PLC) or phosphatidylinositol 3-kinase-γ (PI3Kγ). These pathways, which often act in parallel with members of the MAPK family, result in the release of intracellular calcium from the endoplasmic reticulum. This promotes the assembly of the actin filaments necessary for cytoskeletal changes inherent in movement and phagocytosis. These pathways are similarly regulated by phosphatases.

NFκB, after liberation from the inhibitory molecule IκBα, is transported to the nucleus, where it serves as a transcription factor for pro-inflammatory.

4.7.5 The Inflammasome

The NLR (nucleotide-binding domain and leucine-rich repeat) receptor family has substantial homology to the TLR family and is known to be important in the recognition of *intracellular* PAMPs. These receptors include NOD1 (recognizes gram-negative cell wall components) and NOD2 (recognizes gram-positive and gram-negative cell wall components). They, along with other proteins, can assemble in the cytosol to form the inflammasome. Activation of the inflammasome results in the posttranscriptional processing and release of IL-1β and IL-18 and NFκB activation in innate immune cells.

The inflammasome complex is involved in intracellular PAMP recognition, activation of the NFκB pathway, and IL-1β processing and release.

4.7.6 Interrelationships

The complexity of signal transduction is compounded by the fact that mediators often signal through more than one pathway. IL-6, for example, signals predominately through the JAK/STAT pathway but is known to activate the MAPK pathway as well. Also, in the ICU patient, there are scores of cytokines, chemokines, and other mediators acting simultaneously.

The inflammatory response also affects multiple cellular processes besides the production of inflammatory mediators. Signaling through the TNF superfamily of cell-surface receptors, for example, is highly proapoptotic. This counter-regulatory mechanism helps turn off the inflammatory response once it has begun, by inducing apoptosis in the cells that produce pro-inflammatory cytokines. Similarly, it has been shown that phagocytosis of apoptotic bodies induces an anti-inflammatory phenotype and the production of T_H2-like cytokines by innate immune cells. It is in this setting of overlapping mediators and signaling pathways that clinical regulation of inflammation has proven so difficult.

Apoptosis serves as a negative regulator of inflammation via the death of inflammatory cells and deactivation of phagocytes, which have ingested apoptotic bodies.

4.8 Clinical Immunomodulation: Targeting Hyperinflammation

Given that the presenting signs and symptoms of sepsis are characteristic of a pro-inflammatory state, it is not surprising that the focus of research in immunomodulation has historically involved attempts at attenuation of the inflammatory response. The first target of immunomodulation was endotoxin. In 1982, Ziegler et al. demonstrated a reduction in both all cause and shock-related mortality in adults with sepsis who were treated with an antiserum harvested from healthy donors who had been vaccinated with killed *E. coli*. Later trials using IgG from similarly vaccinated donors and IgG from donors with a high titer to the LPS core antigen showed no benefit. Murine monoclonal antibodies to the lipid-A portion of the LPS molecule were similarly inef-

fective at improving sepsis survival in adults. The initial trial of a human monoclonal antibody did show a reduction in mortality, but a subsequent phase III trial was stopped after an interim analysis showed a trend toward *increased* mortality in some treatment groups.

In an attempt to reduce inflammation through the reduction of circulating IL-1β, recombinant IL-1ra has been administered to adults with septic shock with some initial success. Unfortunately, two large phase III trials in the mid-1990s were not able to demonstrate a survival benefit using rIL-1ra for this indication. Similarly, a large phase II trial of a bradykinin receptor antagonist failed to impact survival in adults with SIRS and gram-negative sepsis. A recombinant form of bactericidal/permeability-increasing protein (BPI), a protein made by activated PMNs which has both antimicrobial and endotoxin-deactivating properties, has undergone a phase III, randomized, controlled trial in children with meningococcemia, which demonstrated an improvement in functional outcome but not mortality.

TNFα has also been a target of immunomodulatory therapy in the ICU. Two studies in the 1990s attempted to use fusion proteins of soluble TNF receptor and IgG to bind circulating TNF and thereby reduce inflammation. Neither was successful at reducing mortality in adult sepsis. Four large anti-TNF monoclonal antibody studies in septic adults have been performed to date. The NORASEPT I and II and INTERSEPT trials all failed to demonstrate improvement in 28-day mortality. The MONARCS trial, conducted in over 2000 adults with severe sepsis, demonstrated a statistically significant reduction in 28-day mortality in the subgroup of patients who had plasma IL-6 levels over 1000 pg/ml, suggesting that patients with a particularly robust inflammatory response may benefit from anti-inflammatory immunomodulation.

Strategies designed to reduce levels of individual circulating pro-inflammatory mediators have largely been unsuccessful in improving mortality in sepsis.

Glucocorticoids represent another class of agents that has been used to reduce the inflammatory response in sepsis. Two meta-analyses published in 1995 evaluated the work of investigators, over the prior two decades, who had given methylprednisolone or dexamethasone to adult patients with sepsis. Both meta-analyses concluded that administration of these glucocorticoids resulted in *increased* mortality in adult sepsis. This can likely be explained by that fact that the anti-inflammatory effects of glucocorticoids also result in immunosuppression, particularly in the large doses used in the earlier trials. It is important to remember that different corticosteroids have different potencies with respect to their anti-inflammatory/immunosuppressive effects (see Table 4.4). Two later meta-analyses suggested a survival *benefit* with the use of low-dose (200–300 mg/day) hydrocortisone in adults with severe sepsis/septic shock. Subsequent clinical trials have yielded conflicting results, and the use of hydrocortisone as adjunctive therapy in sepsis remains controversial. If present, the benefits of hydrocortisone therapy are less likely to be the result of its anti-inflammatory properties than the hemodynamic effects of the drug (i.e., upregulation of catecholamine receptors; mineralocorticoid activity). A prospective pediatric study to address this important topic is ongoing.

Table 4.4 Relative potencies of commonly used corticosteroids

Corticosteroid	Anti-inflammatory effects (immunosuppressive)	Mineralocorticoid effects
Dexamethasone	30	0
Methylprednisolone	5	1
Hydrocortisone	1	5

Lastly, extracorporeal therapies, including hemofiltration, plasmapheresis and plasma exchange, have been used in the setting of sepsis in an effort to provide bulk removal of inflammatory mediators through diffusion, convection, or membrane adsorption. No method has been shown to impart consistent benefit in the setting of sepsis, though most have been evaluated in small studies and employed for short durations. An exception to this is an open-label, randomized, phase II trial of an extracorporeal endotoxin absorber, which was evaluated in 143 adult patients with severe sepsis/septic shock, presumably due to gram-negative infection. Patients who were randomized to the treatment group received the therapy daily for 4 days with no survival benefit seen. Pediatric data indicate that thrombocytopenia-associated multiple organ failure (TAMOF), a phenotype related to thrombotic thrombocytopenic purpura (TTP), may be a target for extracorporeal therapy. Patients with TAMOF have low levels of von Willebrand factor-cleaving protease activity, similar to TTP, contributing to the development of microvascular thrombosis. Both single- and multicenter studies of a prolonged, TTP-based plasma exchange regimen for children with TAMOF have suggested benefit. Of the extracorporeal therapies evaluated in controlled trials to date, plasmapheresis and plasma exchange have the greatest number of reports, indicating a survival benefit, though large randomized, controlled trials are still warranted.

Methylprednisolone and dexamethasone are not indicated for immunomodulation in sepsis. Hydrocortisone therapy may be considered.

Extracorporeal therapies, whose goal is bulk removal of cytokines, have not demonstrated consistent benefit in the setting of hyperinflammation; however, plasma exchange may be helpful in the setting of TAMOF.

4.9 Immunoparalysis

The historic focus on the pro-inflammatory features of critical illness has shifted to include the anti-inflammatory response. For example, while some deaths occur during the first 24–48 h after the onset sepsis, most occur beyond that time frame and often happen in the context of nosocomial infection or unresolving organ failure. An *underactive* rather than overactive innate immune response may be responsible for these adverse events. It has been known for some time that exposure to an inflammatory stimulus leads to a compensatory upregulation of anti-inflammatory cytokines. Numerous investigators have now shown that some patients do not return to normal immune function following an inflammatory insult, but instead develop a persistent, exaggerated anti-inflammatory response, which can be thought of as a type of secondary immunodeficiency.

This state has been termed immunoparalysis and is characterized by reduced expression of HLA-DR on the surface of circulating monocytes as well as an impaired ability of leukocytes to produce pro-inflammatory cytokines when stimulated ex vivo. Reduction of HLA-DR expression on circulating monocytes is associated with increased incidence of secondary infection and mortality in adult critical illness. Modest reductions in antigen presenting capacity can be well tolerated, but when the percentage of monocytes strongly expressing HLA-DR drops below 30%, risks for these adverse outcomes dramatically increase. Marked, persistent reduction in monocyte HLA-DR expression has been reported to be associated with adverse outcomes from trauma, sepsis, and pancreatitis in adults. Studies using a flow cytometric method, capable of quantifying HLA-DR molecules per cell, have suggested a cutoff of <8000 HLA-DR molecules per monocyte to define immunoparalysis in adults. Pediatric data are more limited, though a threshold of <30% monocyte HLA-DR positivity has been shown to be associated with nosocomial infection and death in children with MODS. A discrete threshold of HLA-DR molecules per monocyte has not been identified in children, however, with some investigators suggesting that a failure to increase monocyte HLA-DR expression over time may be more predictive of outcomes from pediatric sepsis than absolute expression thresholds.

Severe critical illness-induced immune suppression (immunoparalysis) is associated with adverse outcomes in the pediatric ICU.

Immunoparalysis is characterized by reduced HLA-DR expression on circulating monocytes and decreased production of TNFα by whole blood when stimulated with LPS ex vivo.

Reduced ability of whole blood to produce TNFα when stimulated ex vivo with LPS has also been shown to be associated with adverse outcomes in critically ill adults and children. A reduced TNFα response indicates hyporesponsiveness of leukocytes to a new challenge, as the response *should* be robust in an immunocompetent individual. Severe reduction in the TNFα response has been associated with increased risks of nosocomial infection, prolonged organ dysfunction, greater severity of illness, and/or death in children with multiple organ dysfunction syndrome, sepsis, trauma, cardiopulmonary bypass, and critical viral infections including influenza. Thresholds of the TNFα response that predict adverse outcomes will vary, depending on the stimulation methods used, and may vary by diagnosis. Standardization of the approach to measurement of the TNFα response will be key to its eventual incorporation into the clinical laboratory.

The adaptive arm of the immune system is also impacted by immunoparalysis. Lymphocyte apoptosis is a common feature of the immunoparalyzed phenotype. This can result in circulating lymphopenia as well as cellular depletion in lymphoid organs such as the spleen. Multiple studies have demonstrated significantly increased risk for the development of nosocomial infection in critically ill children, whose absolute lymphocyte counts are <1000 cells/mm^3, even if otherwise immunocompetent. In addition to a reduction in lymphocyte numbers, critically ill children can demonstrate reduced lymphocyte function as well. Wong et al. performed leukocyte mRNA profiling in a cohort of children with early septic shock and were able to classify subjects into endotypes based on up- or downregulation of genes important in glucocorticoid and lymphocyte signaling. Subjects with a predominately downregulated endotype demonstrated increased risks for prolonged organ dysfunction and death. Similarly, Muszynski et al. showed impairment in lymphocyte cytokine production capacity in septic children who went on to have adverse infectious outcomes.

High systemic levels of pro-inflammatory cytokines have consistently been associated with adverse outcomes from critical illness in adults and children. Wong et al. have been able to derive and validate a panel of serum cytokine biomarkers (the PERSEVERE model) that can risk-stratify children with early septic shock. Elevations in levels of these biomarkers, which include C-C chemokine ligand 3 (CCL3), IL-8, heat-shock protein 70 kDa 1B, granzyme B, and matrix metallopeptidase 8, have been reproducibly associated with mortality using the PERSEVERE model. Immunoparalysis has been associated with elevations in plasma levels of IL-10, and anti-inflammatory cytokine, suggesting skewing toward a T_H2-like state. Anti-IL-10 neutralizing antibodies have been demonstrated to reverse experimental immunoparalysis. Paradoxically, immunoparalysis is also frequently associated with elevated plasma levels of pro-inflammatory cytokines. The simultaneous presence of high systemic levels of inflammation and hyporesponsiveness of circulating leukocytes may be explained by the fact that pro-inflammatory cytokines are produced by injured, stressed, or infected parenchymal cells and vascular endothelium. The ongoing production of these mediators at the tissue level may contribute to the perpetuation of immunoparalysis, as systemic leukocyte function is downregulated in response.

Elevations in systemic levels of pro-inflammatory cytokines can occur simultaneously with immunoparalysis.

Early studies suggested that only a prolonged state of immunoparalysis (lasting >72 h after the initial insult) was associated with adverse outcomes. More recent data have shown that severe reductions in the immune response that occur as early as 24–48 h after the onset of critical illness confer increased risk for nosocomial infection, prolonged organ dysfunction, and/or death.

4.10 Immunoparalysis as a Target of Therapy

Immunoparalysis can be reversed through tapering of exogenous immunosuppression or administration of immunostimulatory drugs, such as recombinant IFNγ or GM-CSF.

Evidence exists that immunoparalysis is not simply an epiphenomenon associated with critical illness, rather it may represent a target for therapy. Rapid tapering of immunosuppression in adult solid organ transplant recipients with sepsis and immunoparalysis has been associated with improved monocyte function and survival of both patient and graft compared with patients whose immunosuppression was maintained. Reversal of immunoparalysis has also been studied in small populations of adults and children with immunoparalysis using drugs, including recombinant GM-CSF and IFNγ. Two small, uncontrolled case series, one using IFNγ and another using GM-CSF, demonstrated normalization of monocyte function in adult sepsis patients with immunoparalysis. Mortality in both cohorts was reduced compared to historical data from immunoparalyzed adults. Rosenbloom et al. demonstrated enhanced clearance of infection in GM-CSF-treated critically ill adults in a 40-subject randomized controlled trial, though a priori immune function testing was not employed. Two small studies, one adult and one pediatric, used prospective immune function testing to identify patients with immunoparalysis, who were then randomized to receive GM-CSF or control therapy. Both showed a greater improvement in monocyte HLA-DR expression and/or TNFα response in GM-CSF-treated subjects, and the pediatric study showed a marked reduction in nosocomial infection in the group that received GM-CSF. Two multicenter pediatric clinical trials of the GM-CSF for the reversal of immunoparalysis are currently underway, including one in pediatric critical trauma (NCT01495637) and one in pediatric sepsis-induced MODS (NCT03769844). The administration of drugs that target restoration of the ability of circulating leukocytes to mount an inflammatory response would seem to carry a risk for promoting inflammation. Reversal of immunoparalysis, however, has been shown to *reduce* systemic inflammation rather than increase it, presumably through restoration the body's ability to clear and repel infection and remodel injured tissues.

4.11 Secondary Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Secondary HLH/MAS represent inflammatory phenotypes that can complicate pediatric critical illness.

Congenital (primary) or acquired (secondary) impairment of NK cell and CD8+ lymphocyte function can result in runaway inflammation, due to an inability of these cytotoxic cells to eliminate activated macrophages and reticuloendothelial cells. The acquired form of this disorder is termed secondary hemophagocytic lymphohistiocytosis (HLH). When it occurs in the setting of rheumatologic disease, it is termed macrophage activation syndrome (MAS), though it is increasingly recognized that HLH and MAS likely represent the same disorder. HLH/MAS is clinically characterized by fever, cytopenias, hepatosplenomegaly, and elevations in laboratory measures that include serum ferritin and soluble CD25. These diagnostic elements also occur frequently in sepsis, making it difficult to distinguish between the two. Direct measurement of NK cell function and/or genotyping can help distinguish between sepsis and HLH/MAS, but the turnaround time is often too long for such testing to be clinically useful. Carcillo et al. have demonstrated, in single- and multicenter observational studies, that marked hyperferritinemia can identify children at high risk of mortality from sepsis. Their work also shows that the inflammatory phenotype of HLH/MAS can be coincident with TAMOF and/or immunoparalysis, suggesting that more than one phenotype-specific therapy may be

required for a given patient. While it is not clear that sepsis-induced hyperferritinemia and HLH/MAS should be treated similarly, it is noteworthy that HLH-style treatment regimens, including the drug anakinra, have been used with some success in this setting.

4.12 Critical Illness and the Inflammatory Response

4.12.1 The Impact of Critical Illness

End-organ dysfunction can affect the production and clearance of immune mediators as well as the production of immunologically active byproducts. Hepatic failure, for example, leads to impaired metabolism of pro-inflammatory cytokines, resulting in an inflamed state. Extracorporeal therapies such as dialysis, with prolonged contact of blood elements with plastic tubing and membranes, lead to the activation of complement. Transfusion of blood products, particularly packed red blood cells, has also been implicated as a source of both inflammation and immune suppression in the critically ill patient. Chronic renal failure leads to an upregulation of parathyroid hormone, which itself impairs B cell proliferation and antibody production as well as impairing neutrophil function. Plasma from uremic patients, typically high in pro-inflammatory cytokines, is also a potent promoter of apoptosis in lymphocytes and PMNs. Hyperglycemia is another common finding, which is associated with inflammation in the ICU. Ample experimental and clinical evidence indicates that glucose can serve as a potent activator of the inflammatory response through potentiation of the NFκB pathway in innate immune cells. Insulin administration results in anti-inflammatory effects indirectly through the reduction of serum glucose and through direct inhibition of the NFκB pathway.

Hepatic failure, hyperglycemia, and extracorporeal therapies can all potentiate the inflammatory response.

Lastly, the stress of critical illness itself can be immunosuppressive through the activation of the hypothalamic-pituitary-adrenal axis and the actions of catecholamines. As noted above, endogenous glucocorticoids contribute to the compensatory anti-inflammatory response syndrome through their inhibition of NFκB signaling. Stimulation of β-adrenergic receptors on innate immune cells results in the upregulation of anti-inflammatory mediators including IL-10. This process is particularly prominent in the setting of brain injury.

4.12.2 Effects of the ICU Pharmacopeia

Many drugs commonly used in the ICU impact the inflammatory response in ways that may not be obvious.

Some drugs, such as NSAIDs, glucocorticoids, calcineurin inhibitors, chemotherapeutic agents, and others, are used to intentionally induce immunosuppression or reduce inflammation. Conversely, hematopoietic stem cell factors, including GM-CSF, are used to promote a more vigorous immune response. A great many of the drugs that are used in the course of daily ICU care, however, have occult immunologic properties. While these drugs are being used for other purposes, it is likely that their cumulative effects modulate the host immune response in unintended ways. Representative drugs and their immunologic effects are listed in Table 4.5.

Table 4.5 Immunologic effects of commonly used ICU medications

Drug/class of drugs	Potential effect on the inflammatory response	Mechanism
Antibacterial agents	Potentiation	Release of bacterial components at the time of cell death
		Direct enhancement of intracellular killing (β-lactams)
	Attenuation	Bone marrow suppression (β-lactams)
		Decreased pro-inflammatory cytokine production (macrolides)
Benzodiazepines	Attenuation	Upregulation of the endogenous cortisol axis
Catecholamines[a]	Potentiation	Stimulation of α-adrenergic receptors
	Attenuation	Stimulation of β-adrenergic receptors
Furosemide	Attenuation	Reduced production of pro-inflammatory cytokines by mononuclear cells
Insulin	Attenuation	Indirect reduction in hyperglycemia-induced pro-inflammatory cytokine production
		Direct inhibition of the NFκB pathway
Opiates	Attenuation	Suppression of IFN production
		Induction of lymphocyte apoptosis
		Induction of macrophage apoptosis
		Induction of TGFβ

[a]In the event that both α and β receptors are stimulated (e.g., epinephrine), the immunologic β effects predominate

4.13 Summary and Future Directions

It is now clearly recognized that the balance between pro- and anti-inflammatory forces is crucial in critical illness and that imbalances in either direction increases the risk for adverse outcomes. Patients who suffer an inflammatory insult do not predictably benefit from therapies aimed at reducing inflammation. Rather, surveillance for, and reversal of, immunoparalysis represents a personalized medicine approach that has the potential to restore immunologic balance in critically ill children. The bulk of the work done in this area has focused on the restoration of innate immune function. The restoration of the adaptive immune response in immunoparalysis is beginning to be studied in septic adults. A dose-finding clinical trial of an antibody targeting programmed death ligand (PD-L)-1 was recently conducted, demonstrating that high-dose

anti-PD-L1 therapy could achieve receptor saturation and may improve immune function. Randomized controlled trials of drugs designed to preserve or enhance lymphocyte function (including targeting of the PD-1 pathway) are still needed in critically ill adults and children. Lastly, most of the tests that are performed to measure inflammatory mediators and to survey for immunoparalysis are limited to research use only. Following larger clinical trials, it will be necessary to move these tests to the clinical laboratory in order to bring therapies targeting restoration of immune function in critical illness to the bedside.

Review Questions

1. The innate immune system is notably different from the adaptive immune system in that innate immune cells:
   A. Do not express toll-like receptors on their surfaces
   B. Produce T_H2-like cytokines upon initial interaction with endotoxin
   C. Require thymic selection to prevent self-reactivity
   D. Respond more vigorously to antigen with repeated exposures
   E. Are typically the cells which initiate the immune response to pathogens

2. The pro-inflammatory mediator or signaling molecule which is *incorrectly* matched with its inhibitor is:
   A. C3a: C5a
   B. NFκB: IκBα
   C. STAT1: SOCS1
   D. MAP kinases: phosphatases
   E. IL-1β; IL-1ra

3. Inhibiting the action of the following mediators of inflammation in the plasma has resulted in consistently improved outcomes in the setting of sepsis:
   A. TNFα
   B. IL-1β
   C. Bradykinin
   D. LPS
   E. None of the above

4. The state of immunoparalysis is characterized by all of the following *except*:
   A. Association with the compensatory anti-inflammatory response syndrome
   B. Reduced monocyte HLA-DR expression
   C. Impaired production of TNFα upon ex vivo whole blood stimulation with LPS
   D. Irreversibility
   E. Association with mortality in the ICU

5. Which of the following drugs has been used for the purpose of immunomodulation in children with hyperferritinemic sepsis?
   A. IFNγ
   B. GM-CSF
   C. Anakinra
   D. Activated protein C
   E. Tacrolimus

Answers

1. E

   Innate immune cells, including PMNs, monocytes, macrophages, dendritic cells, and NK cells, are typically the immune effector cells which first recognize pathogens and initiate the inflammatory response. They do so by virtue of cell-surface receptors such as the toll-like receptors, which recognize pathogen-associated molecular patterns. The activation of the innate immune response is not associated with a memory response. Immunological memory is a feature of the adaptive immune system. The cytokines produced by innate immune cells upon initial exposure to endotoxin include TNFα and IL-1β. These cytokines are typical of T_H1 polarization. T lymphocytes undergo positive and negative selection in the thymus to minimize self-reactivity.

2. A

   Unregulated inflammation would quickly result in the death of the host. Accordingly, inhibitory pathways have evolved to provide negative feedback for most pro-inflammatory systems. IκBα, the SOCS family of proteins, and phosphatases serve as important negative regulators of the NFκB, JAK/STAT, and MAP kinase signaling pathways, respectively. IL-1ra is an example of a circulating inhibitor that competes with IL-1β for receptor binding. The complement system likewise is inhibited by an array of molecules, including the cell-surface proteins CR1, MCP, and DAF along with circulating inhibitors, such as factor I, factor H, and C4-binding protein. C3a and C5a are both anaphylatoxins, cytokines which result in increased vascular permeability, increased endothelial molecule expression, and phagocyte recruitment.

3. E

   Reduction in plasma concentrations of, or inhibition of receptor activation by, all of aforementioned mediators has been attempted in the setting of sepsis. Administration of anti-LPS IgG (pooled), murine monoclonal anti-LPS antibodies, recombinant IL-1 receptor antagonist, a bradykinin receptor antagonist, and anti-TNFα antibodies has not resulted in consistently reproducible improvement in mortality in the setting of sepsis. Evidence exists that a subset of patients with particularly pronounced inflammation may benefit from anti-TNFα antibodies, but their use is currently not the standard of care.

4. D

   Immunoparalysis represents an exaggerated compensatory anti-inflammatory response, which is characterized by reduced monocyte HLA-DR expression (with <30% of circulating monocytes being strongly HLA-DR positive) and reduced production of TNFα upon ex vivo stimulation of whole blood with LPS. A persistent state of immunoparalysis has been associated with increased mortality, persistent organ failure, and the development of secondary infection in adults and children. Immunoparalysis has been shown to be reversible through the tapering of exogenous immunosuppression or administration of T_H1-like cytokines, including IFNγ and GM-CSF. Evidence for the clinical benefit of the reversal of immunoparalysis is currently limited to small case series.

5. C

Anakinra, or recombinant IL-1 receptor antagonist, is part of some treatment regimens for HLH/MAS and has been used in children with hyperferritinemic sepsis. It targets IL-1β production by overactive macrophages and reticuloendothelial cells and may reduce symptoms of hyperinflammation in this setting. IFNγ and GM-CSF are both T_H1 cytokines that can be administered in recombinant form for the reversal of immunoparalysis. Neither activated protein C nor tacrolimus has a role in the management of sepsis or HLH/MAS.

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Nutrition in Critical Illness

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Contents

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5

Learning Objectives

- Understand the nutritional requirements of healthy children and how these are modified for critically ill children in the PICU.
- Be able to utilize available formulas and methods to determine caloric and protein needs of PICU patients.
- Be able to make appropriate choices for the provision of nutritional support to patients based on their disease state and clinical status.
- Be able to apply appropriate means for evaluating adequacy of nutritional support and make clinically relevant adjustments.
- Understand the principles of nutritional support for patients with specific disease states such as intestinal insufficiency, liver disease, renal insufficiency, as well as the principles of immunonutrition.

5.1 Nutrition in Healing

Malnutrition is common among PICU patients.

Provision of appropriate nutrition to ill children is fundamental to their recovery. Earlier studies have found that up to one quarter of children in the PICU are malnourished on admission or become nutritionally deprived during admission. Malnutrition in the PICU—whether premorbid or iatrogenic—is associated with longer hospital stays and poor outcome. Moreover, data suggest that malnutrition, either acute or chronic, is associated with physiological instability including impaired immune function and impaired ventilatory drive resulting in the need for increased quantity of care. Caloric intake to provide the body with sufficient energy to perform cellular activity, adequate protein intake for maintenance of cellular function and wound healing, and specific nutrients for biochemical functions are necessary in providing comprehensive care of the ill or injured child. In addition, the growth needs of children must be recognized and accounted for in providing protein, energy and nutrients. However, barriers to providing adequate nutrition exist in the critical care setting. These barriers include the need for fluid restriction, gastrointestinal intolerance (e.g., emesis, residuals, diarrhea), interruption of feeds for procedures, and hemodynamic, respiratory, or metabolic instability which may delay initiating nutritional support.

5.2 Determining Nutritional Needs

5.2.1 Energy

Metabolism downregulates in simple calorie malnutrition but increases in malnutrition associated with critical illness.

Calorie requirements are composed of the resting energy expenditure (REE), also known as basal energy expenditure (BEE), and the additional energy needed for activity, growth, and, in the ill child, healing from wounds or disease. A healthy child in the well-fed state favors anabolism and growth with high levels of insulin and growth hormone and low levels of glucagon and other counter-regulatory hormones. In individuals deprived of calories and nutrients, the metabolic machinery of the body downregulates, thereby effectively reducing energy expenditure to conserve fuel and ameliorate weight loss. Initially, glycogen stores (in the liver and skeletal muscle) are consumed to readily provide glucose. Later in the process of calorie malnutrition, ketones are synthesized from the oxidation of fat stores, producing ketone bodies which can be used for energy by most tissues. However, some body cells and tissues such as red and white blood cells and the myocardium require glucose for energy, necessitating consumption of amino acids from somatic (muscle) and visceral (organ) protein for gluconeogenesis. This process results in muscle wasting, visceral protein compromise, and excessive nitrogen loss.

Obesity is an increasingly prevalent issue for patients of all ages and can be a significant comorbidity in intensive care situations. Obesity in the pediatric critical care unit has been associated with higher risk of hospital-acquired infections, longer length of stay, and mortality although this assertion is disputed elsewhere in the literature. Assessing the calorie needs of obese children in the critical care unit is challenging and can result in over- or undernutrition when standard formulas are used.

In critically ill patients in the PICU with increased metabolic stress, high levels of counter-regulatory hormones (glucagon and cortisol) counteract the normal energy-conserving compensatory mechanisms resulting in accelerated loss of energy stores. Historically it had been assumed that ICU patients have increased calorie requirements. However, studies in both adults and children have not supported this concept. In fact, the adult critical care literature consensus as well as the most recent (2016) joint American Society for Parenteral and Enteral Nutrition (ASPEN) and Society of Critical Care Medicine (SCCM) guidelines caution against overfeeding calories to the critically ill adults. Indeed, two small pediatric ICU studies, utilizing indirect calorimetry (see below) for measurement of energy expenditure, demonstrate frequent overprescription of calories for critically ill children. However, practice in Pediatric Critical Care Medicine remains divided as to whether the critically ill patient in the PICU requires more or less energy than would be predicted by common measures applied to healthy children.

In practical terms, the determination of calorie requirements for individual PICU patients is challenging and fraught with inaccuracy. From the most technically demanding measures using indirect calorimetry to simple tables and equations based on anthropometric data, many methods exist for estimating calorie requirements, and all have limitations. However, an effort must be made early in the course of illness to determine the energy needs of each patient, to set nutrition goals, and to attempt to attain them.

There is no consensus regarding whether pediatric patients in the ICU have increased or decreased calorie needs over baseline. Factors that contribute to increased calorie need are head trauma and older age; factors that predict lower calorie need are younger age and the use of muscle relaxants.

5.2.2 Calorimetry

Indirect calorimetry involves the measurement of resting energy expenditure (REE) by measuring the difference in oxygen (O_2) and carbon dioxide (CO_2) contents between a known volume of inspired and expired air. This method, although considered the most accurate, is technically demanding and time-consuming, involves the use of expensive specialized equipment that is not universally available, and requires trained personnel. In order to obtain accurate information, the patient must be on a ventilator with stable ventilator settings during the period of measurement. The accuracy of the measurement is impaired when the patient requires a fraction of inspired oxygen (FiO_2) of 0.6 or greater and if there is endotracheal tube leak. In addition, the test assumes stable energy utilization throughout the analysis. The patient should be at rest without active nursing care or transports during the measurement. The device will measure oxygen utilization (VO_2) and carbon dioxide production (VCO_2) and calculate the REE using the modified Weir equation:

$$\text{REE} = \left[\text{VO}_2 \left(3.941\right) + \text{VCO}_2 \left(1.11\right) \right] \times 1440\,\text{min}$$

where REE is in Kcal/day and VO_2 and VCO_2 are measured in ml/min. Guidelines for the use of REE measurement in critically ill children include recommendation for indirect calorimetry in specific critically ill populations, including mechanical ventilation greater than 7 days, greater than 10% weight gain or loss during critical illness, and anticipated hypermetabolic or hypometabolic states.

The most accurate method for evaluating patient energy requirement is using indirect calorimetry, which measures oxygen utilization and carbon dioxide production to determine calories.

5.2.3 Respiratory Quotient

The results of the calorimetry measurement can also be used to determine the respiratory quotient (RQ). This is a measure of the ratio of expired CO_2 produced to inspired O_2 consumed. This ratio estimates the state of calorie usage in the patient. RQ represents a combination of various ratios of oxidative and reductive processes. It is specific and constant for the oxidation of fat, carbohydrate, and protein as well as lipogenesis. The metabolism of carbohydrates, for example, results in an RQ of 1.0 (for every carbon dioxide molecule produced, one oxygen molecule is utilized), whereas the RQ for the metabolism of lipid approaches 0.6, and the RQ for protein alone is 0.8. A typical mixed diet results in an RQ of approximately 0.8.

$$RQ = VCO_2 / VO_2$$

A nutrition regimen of higher fat content will result in a lower RQ, which may be advantageous for patients with CO_2 retention and difficulty weaning from the ventilator. A diet high in carbohydrates results in an RQ closer to 1.0 and, therefore, should be avoided in problematic hypercarbia.

5.2.4 Fick Equation

An alternative method for measuring caloric utilization is based on the Fick equation, which uses the cardiac output determined from a pulmonary artery (PA) catheter, the hemoglobin concentration, and the arterial and venous oxygen concentrations to calculate the REE:

$$REE = CO \times Hb \times \left(SaO_2 - SvO_2\right) \times 95.18$$

where REE is calculated in Kcal/day, CO is cardiac output in L/min, Hb is hemoglobin in g/dL, and SaO_2 and SvO_2 are the arterial and venous oxygen saturations, respectively.

Given the infrequency that PA catheters are utilized in pediatric critical care, this option remains a theoretically interesting but impractical alternative. With newer technologies, such as PiCCO, such measurements are more feasible, but this application has not been evaluated.

Measuring calorie needs by indirect calorimetry or by using PA catheter data, while perhaps more accurate, is cumbersome, and most PICUs do not have the machinery necessary. However, recently, a calculation to determine calorie needs based on VCO_2 alone has been developed and validated.

$$REE = 5.5 \times VCO_2 \times 1440$$

Here, REE is measured in Kcal/day and VCO_2 is measured in L/min. The advantage of this formula is that VCO_2 can be obtained from the most modern ventilators, and so this accurate estimation of energy needs can be done on any ventilated patient.

5.2.5 Formulas and Tables

Standard dietary guidelines are an appropriate starting point for determining micronutrient needs.

Recognizing that indirect calorimetry requires expensive machinery and technological capability, perhaps the most useful, inexpensive, and widely applicable method to determine the calorie needs of a child is to employ population-based tables (see Table 5.1). These tables are based on population studies of healthy persons and provide a rough guideline for initiating a

Table 5.1 Currently available methods to determine the estimated calorie needs of children and adults

Reference	Subject age (years)	Subject #	Site	Equations	Factors
World Health Organization	0–3	>11,000	Data taken from previously published work in developed and underdeveloped countries	Male: 60.9(W) – 54	Weight, age, gender
				Female: 61.0(W) – 51	
	3–10			Male: 22.7(W) + 495	
				Female: 22.5(W) + 499	
	10–18			Male: 17.5(W) + 651	
				Female: 12.2(W) + 746	
	18–30			Male: 15.3(W) + 679	
				Female: 14.7(W) + 496	
	30–60			Male: 11.6(W) + 879	
				Female: 8.7(W) + 829	
	>60			Male: 13.5(W) + 487	
				Female: 10.5(W) + 596	
Schofield	0–3	>11,000	Re-analysis of WHO data	Male: 0.167(W) + 1517.4(H) – 617.6	Weight, height, age, gender
				Female: 16.252(W) + 1023.2(H) – 413.5	
	3–10			Male: 0.082(W) + 0.545(H^*) + 1.736	
				Female: 0.071(W) + 0.677(H^*) + 1.553	
	10–18			Male: 0.068(W) + 0.574(H^*) + 2.157	
				Female: 0.035(W) + 1.948(H^*) + 0.837	
	18–30			Male: 0.063(W) – 0.042(H^*) + 2.953	
				Female: 0.057(W) + 1.184(H^*) + 0.411	
	30–60			Male: 0.048(W) – 0.011(H^*) + 3.670	
				Female: 0.034(W) + 0.006(H^*) + 3.530	
	>60			Male: 0.038(W) + 4.068(H^*) – 3.491	
				Female: 0.033(W) + 1.917(H^*) + 0.074	

Calorie estimation can be based on age, height, weight, and sex. The most commonly used formulas are provided. In practice, a factor is included to account for normal daily activity. The other formulas listed are for total calorie expenditure per day. *A* age in years, *W* weight in kg, *H* height in cm, H^* height in m

nutrition plan for the patient in the PICU. Reliable sources include the World Health Organization (WHO) data and the Schofield formula. However, recent recommendations discourage the use of "stress factors" with these tables as this often leads to over calculation of calorie requirements and overfeeding in patients who may be hypometabolic. Two small studies utilizing indirect calorimetry in critically ill children demonstrated overfeeding in 60% and 80% of

children with calorie prescription guided by standard equations. Indeed, no available formula or table is able to accurately take into consideration whether the patient is in a hyper- or hypometabolic state or account for medical interventions, such as mechanical ventilation, inotropes, neuromuscular blockade, and sedation. While the Harris Benedict equation and the United States Recommended Dietary Allowances are also readily available for establishing calorie needs in children, their use is not recommended in the critical care setting as they provide data for healthy children only. Despite these limitations, formulas and tables are simple to use and require no equipment more complicated than a measuring tape or scale. Moreover, the application of these simple methods provides health-care providers with a starting place and a goal for nutritional support.

5.3 Protein and Nitrogen Balance

Calculation of nitrogen balance can be used to determine protein requirements.

Because of the potential hypermetabolic state of critically ill children and the hormonal milieu favoring catabolism, it is anticipated that these patients will be consuming somatic and visceral protein to supply increased enzyme and energy needs. As with overall energy needs, determination of protein requirements is equally challenging and similarly controversial. As a rule, a minimum of 1.5 grams of protein per kilogram of lean body mass is recommended. The USRDA (1989) and WHO tables based on healthy children provide estimates but, unfortunately, less accurate estimations than can be obtained using more sophisticated techniques. For example, a more accurate method for determining protein requirements in the hospitalized child is to measure nitrogen balance. This method determines nitrogen loss by measuring 24-hour urinary nitrogen in combination with estimates of gastrointestinal nitrogen excretion. This result is used to extrapolate protein utilization and, thus, protein requirement. Patients with exposed dermis or weeping wounds and excessive gastrointestinal losses and patients on renal replacement therapy, dialysis, or plasmapheresis will have nitrogen losses that cannot be accounted for. As with overall caloric determination, the dynamic nature of the critically ill child mandates frequent reassessment to determine protein intake requirement regardless of the method used.

Calculation of protein requirement via urinary nitrogen is based on the concept that most nitrogen excreted from the body is a result of protein turnover. The bulk of this excretion occurs from the kidney in the form of urea, which is synthesized from nitrogenous waste in the liver. Protein is approximately 16% nitrogen by weight; therefore, every gram of nitrogen in the urine represents 6.25 g of protein broken down. In addition to urinary nitrogen loss, nitrogenous waste in the stool must be estimated. Protein loss from surgical, traumatic, and burn wounds cannot be directly measured and must be estimated empirically. Normally, nitrogen balance should approach zero. The discrepancy between intake and output should be addressed by adjusting protein content of the diet.

Of importance, as well, is the nonprotein calorie to nitrogen ratio (NPC:N_2). This simple calculation compares the calories from fat and carbohydrate with the total nitrogen content of the feeding (either parenteral or enteral). The equation is as follows, where the subtraction of 4 converts from total calories to nonprotein calories per gram of protein in the prescribed tube or intravenous preparation:

$$\text{NPC} : \text{N}_2 \text{ ratio} = \left(\text{total calories per gm protein} - 4\right) \times 6.25 \,\text{gm protein}$$

Outside of critical illness, the ratio, which is effectively a measure of the number of calories required to appropriately metabolize a gram of nitrogen, is 150:1–250:1 and should not fall below 100:1. At lower levels, the amino acids in the protein will be catabolized to provide calories, and the nitrogen will be discarded adding to the nitrogen stress of the patient. A recent randomized controlled trial of protein supplementation in critically ill children showed positive nitrogen balance only in the protein-supplemented group (3.1 gm/kg/day) compared with controls (1.5 gm/kg/day) with calories held constant. Of interest, the NPC:N_2 ratio was 129 in the protein-supplemented group compared with 256 in the standard formula group. This is consistent with the preponderance of evidence in adult critical care nutrition studies and current SCCM/ASPEN guidelines focusing on protein intake to achieve positive nitrogen balance in critical illness.

5.4 Micronutrients

The provision of additional vitamin C, zinc, and selenium promotes wound healing and increases antioxidant capacity.

Micronutrients include vitamins and minerals. These are essential as cellular intermediaries, enzyme cofactors, and antioxidants and are often deficient in critically ill children. Guidelines for the provision of micronutrients in critical illness in children are lacking. In general, micronutrient needs are best met using standard formulations, which usually approximate recommended dietary allowances. The assessment of nutrient deficiencies in critically ill patients is difficult given the variety of metabolic stresses, increased nutrient losses, decreased nutrient absorption, disordered nutrient distribution, and disordered homeostasis. For some minerals, such as calcium, phosphorus, and magnesium, plasma levels can and should be used to determine individual patient needs. Iron, copper, and zinc levels are measured much less frequently; however, supplementation of these and most other vitamins and trace elements is done on an empiric basis.

Micronutrients of particular interest in the PICU patient include those that have antioxidant properties and those that promote wound healing. Critically ill patients are known to have increased oxidative stress, exogenously, from exposure to high doses of oxygen via mechanical ventilation or supplemental oxygen, and endogenously, from the generation of free radicals in the face of injury and inflammation. In addition, wound healing, whether from trauma, surgical procedures, or decubitus ulcers, is dependent on specific nutrients. While the administration of a multivitamin to provide the recommended dietary allowance of all essential vitamins and minerals is a widely accepted practice in PICU care, extra supplementation of some nutrients may be advisable. *Vitamin C* has many biochemical functions including collagen formation, biosynthesis of bile and catecholamines, and antioxidant properties, all of which are beneficial for the recovering patient. Vitamin C levels have been shown to be low, and turnover increased in patients with critical illness; therefore, supplementation of vitamin C above the standard dose is advisable. *Vitamin E* functions as an antioxidant and is useful in maintaining cell membrane integrity as well as cellular immunity. The recommendation for the dose of vitamin E supplementation is controversial; however, supplying at least the RDA is considered prudent. The *selenium* requirement increases in critical illness as a result of increased cellular uptake and increased urinary loss. Supplementation of selenium (2 micrograms per kilogram per day) is recommended. *Zinc* is known to assist in wound healing in burn patients; zinc supplies in the critically ill patient are generally low as a result of increased urinary losses. In addition, patients with poor wound healing and burns have been found to have

low tissue zinc levels, and zinc supplementation has been associated with improved lymphocyte counts in critically ill children. Zinc supplementation, therefore, is prudent in critically injured patients, particularly those with wounds or bodily injury. In summary, a multivitamin with trace minerals (enteral or IV) should be standard protocol for all PICU patients with additional zinc, selenium, and vitamin C provided. *Vitamin D* deficiency has been studied recently as a cofactor in poor outcomes in the PICU due to its important role in macrophage, lymphocyte, and epithelial cell function. Vitamin D deficiency is common among critically ill children and correlates with increased severity of illness.

5.5 Immunonutrition

Immunonutrients such as nucleotides, lactoferrin, omega-3 fatty acids, arginine, and glutamine may enhance immune health but have not been found to improve outcomes in ICU patients.

One of the more interesting lines of research in this area is the idea of "immunonutrition," which posits that critically ill patients have immune dysregulation and that provision of particular nutrients may improve immune function, and infectious complications have been shown to be reduced in adult patients receiving formulas with immune-promoting components. These components include nucleotides, omega-3 fatty acids, glutamine (thought to be specifically protective of gastrointestinal mucosa), and arginine, a precursor of nitric oxide. In addition, probiotics and lactoferrin are considered beneficial in the immune health of infants and children. Although early research using these principles is promising, a meta-analysis of available literature does not support the claim of improved survival in patients given a formula rich in the so-called immunonutrients. The most recent critical care nutrition guidelines for adults from SCCM and ASPEN do encourage the use of certain micronutrients in selected circumstances (e.g., omega-3 fatty acids in traumatic brain injury).

5.6 Monitoring

Serum prealbumin and retinol-binding protein are more accurate measures of visceral protein stores than albumin and are not affected by fluid status.

The monitoring of the overall nutritional status of the outpatient is usually achieved with basic height and weight measurements over time and comparing these to national standards. While this is sufficient for the ambulatory patient, in the PICU, these measurements have limited value. Weight is highly variable from day to day in the critical care setting, and it is influenced by non-nutritional factors, such as fluid state and wound dressings, monitor leads, and other equipment. Although older children are not typically in the PICU long enough for stature to be a useful metric for acute nutritional status, in infants, length and head circumference should be measured and plotted on standard growth curves on a regular basis with the goal of maintaining a normal pace of growth. Other less commonly performed anthropometric measurements, such as arm circumference and triceps skinfold, are prone to inaccuracy in critically ill patients as these can be affected by edema.

In addition to determining nitrogen balance as previously described, the measurement of visceral proteins is a useful surrogate for protein status in the acutely ill patient. Typical visceral proteins measured are albumin, prealbumin and retinol-binding protein. The value of serum albumin measurements as a nutritional parameter is limited because of its long half-life and because these levels are influenced by the hydration status of the patient and whether exogenous albumin has been used as a volume enhancer. Other serum proteins such

as ferritin and transferrin will fluctuate widely in the face of acute inflammation and injury. Prealbumin and retinol-binding protein have been thought to be more accurate measures of visceral protein stores however they too can be influenced by physiologic factors. Prealbumin, which is named because of its proximity to albumin on an electrophoretic strip, functions in the transport of thyroxine and has a half-life of 24 to 48 hours and is more commonly used in nutrition evaluation. It is produced in the liver, and as such, its concentration may be decreased in liver disease. Prealbumin levels will be suppressed in response to systemic inflammation as a sign of acute catabolism. A consensus statement from the Academy of Nutrition and Dietetics (AND) and ASPEN noted that prealbumin is an indicator of inflammation and lacks the specificity to diagnose malnutrition. Indeed, studies have demonstrated a negative correlation between C-reactive protein (CRP) and prealbumin levels. Nevertheless, prealbumin level can be used as a surrogate for nitrogen balance, measuring visceral protein synthesis, during recovery as systemic inflammation subsides and nutritional repletion is established. One additional caveat to the use of prealbumin is its elevation in response to pharmacological doses of corticosteroids, disassociating its level (at times quite high) from overall nitrogen balance. The total lymphocyte count has been historically found to fluctuate with nutritional status and so can be used to assess nutritional status. However, in patients with immunodeficiency, either innate or acquired, a more and more common comorbidity in the PICU, low lymphocyte counts may not reflect nutritional status alone. In patients on parenteral nutrition, daily measurement of minerals, such as electrolytes, calcium, phosphorus, and magnesium, is essential in order to make appropriate adjustments to their formula. The measurement of other micronutrient levels and trace minerals should be performed based on the clinical features of the patient.

5.7 Glycemic Control

Hyperglycemia is seen in critically ill adults and children. Historically, this was accepted as a compensatory hormonal response to illness, and glucose levels in the 200 mg/dL range were accepted. Earlier studies demonstrated improved outcomes in adult ICU patients when glycemia was more tightly controlled with insulin. However, an international, multicenter trial (NICE-SUGAR Study) that randomized over 6000 critically ill adults to either tight glucose control (target glucose level 81–108 mg/dL (4.5–6.0 mMol/L)) or conventional therapy (target glucose level less than or equal to 180 mg/dL (10.0 mMol/L)) found that tighter glucose control resulted in increased mortality. More recent studies have had varying results with some indicating a benefit to tight glycemic control while a meta-analysis evaluating glycemic control indicated increased incidence of hypoglycemia in treated patients and no benefit with regard to mortality or acquired infections. Some post hoc analyses of the studies have pointed out the high use of TPN, contributing 87% of calories, in the studies purporting to demonstrate benefit, suggesting that TPN-related hyperglycemia may have increased mortality in the control groups. The prospective randomized controlled trial of tight glucose control in 35 pediatric intensive care units (HALF-PINT Study), performed in conjunction with the Pediatric Acute Lung Injury and Sepsis Investigators Network (PALISI), noted a higher rate of complications and no benefit of tight glucose control in children. Clinical equipoise is recommended when employing this strategy.

5.8 Nutrition Delivery

In general, the literature supports early initiation of enteral or parenteral nutrition for critically ill children in the PICU. The advantages of this practice include maintenance of gastrointestinal integrity, reduced incidence of multiorgan dysfunction, and reversal of a hypermetabolic state, and clinical studies typically show a correlation between early nutrition and improved outcomes. However, in the most acutely ill patients, there is evidence that nutrition may not be useful because the patient is highly catabolic and cellular metabolism is counter-regulatory with evidence of insulin resistance. In this scenario, nutrient supplies go unused and hyperglycemia may result. Nevertheless, given the preponderance of evidence in the literature supporting early feeding and recognizing that advancing to full calories may take several days, early feeding of patients in the PICU is encouraged whenever feasible.

5.9 Enteral Nutrition

Either parenteral or enteral nutrition can be used safely in the PICU; however, the preponderance of evidence suggests that enteral nutrition is superior.

Various studies have been conducted examining the risks and advantages of enteral nutrition with overwhelming support for use of the enteral route whenever possible. An earlier meta-analysis of the adult literature assessing the use of parenteral versus enteral nutrition found that nutritional outcomes between the groups were similar (nitrogen balance, weight gain); however, the enteral group had fewer overall complications. More and more, in pediatrics, early enteral nutrition is favored.

The advantages of enteral nutrition include the maintenance of gastrointestinal health, its ease, and its low expense. The provision of feedings directly to the gastrointestinal mucosa has been found to maintain brush border enzyme integrity and prevent gut atrophy. This results in the prevention of translocation of enteral bacteria, which may result in sepsis. Also, enteral feedings reduce cholestasis and promote normal hepatic and portal vein function. In addition, supplying nutrients directly to the alimentary tract allows the body to regulate nutrient intake using natural feedback mechanisms.

Nevertheless, there are contraindications to the use of enteral nutrition in the critically ill patient. The so-called absolute contraindications include mechanical failure of the gastrointestinal tract including ileus, bowel obstruction, gastrointestinal bleeding, and simple intolerance of feedings. Conditions of decreased gut profusion, such as infantile coarctation of the aorta, with compromised intestinal perfusion, also represent a contraindication to enteral feedings. In addition, most practitioners have a list of relative contraindications to feeding the gastrointestinal tract, which may include the use of vasopressor infusions, such as epinephrine, norepinephrine, or vasopressin, pancreatitis, recent hypoperfusion states such as hypotension and shock, lack of airway protection, or postoperative patients undergoing facial reconstruction for whom emesis could be dangerous or injurious to surgical wounds. Recent data suggest that the danger of enteral nutrition in patients on vasopressors is unfounded and that these patients tolerate enteral feeding with no difference in adverse outcomes. Patients on ECMO are successfully fed enterally, but their gastrointestinal health must be closely monitored as gut perfusion may be compromised on bypass.

Enteral feedings can be supplied via the stomach or the small bowel. Nasogastric tubes can be easily placed at the bedside and are typically well tolerated. When this is not possible, such as with gastric dysmotility, a transpyloric tube can be inserted nasally by bedside personnel or under fluoroscopy in interventional radiology.

5.10 Enteral Formulas: Standard

Enteral nutrition is supplied either orally in the healthier patients or through nasogastric, naso-duodenal (jejunal), or surgically placed enterostomal devices. The placement of a nasal feeding tube is inexpensive, relatively easy, and minimally traumatic to the patient. The wide variety of enteral formulations on the market worldwide facilitates tailoring the formula to the specific needs of the child. A dietitian on the PICU team can be of great value in determining the best formula for a particular patient.

Standard pediatric enteral nutrition formulas contain approximately 45–55% of calories as carbohydrate, 34–43% as fat, and 12% as protein.

Patients who lack specific digestive and absorptive deficiencies (i.e., normal digestion) should be started on standard age-appropriate formulas. There are a multitude of infant and child formulas available, which contain the appropriate proportions of calories to protein and micronutrients. In addition, expressed breast milk can also be provided for infants via an enteral tube. Most formulas are cow milk based and contain a greater proportion of protein from whey than from casein to mimic human breast milk. Most of these formulas also contain added taurine, which is a provisional essential amino acid for infants. Nutrition supplements for children are similarly formulated to meet the needs of the healthy ambulatory child. Thus, a typical standard tube feeding formula available for critically ill children is one formulated for healthy infants and children. It will be fortified with essential vitamins and minerals and contain approximately 45–55% of calories from carbohydrate, 34–43% from fat (including the essential fatty acids arachidonic, linoleic, and linolenic acids), and 12% from protein. The specific ingredients and age-appropriate nutrient variations differ among manufacturers. However, these standard pediatric formulas are relatively low in protein for the critically ill child. While there are a number of tube feeding formulas for critically ill adults, which can be used in the older child or adolescent, there are no tube feeding formulas developed for the critically ill infant and toddler. Most currently available pediatric tube feeding products have 12% calories from protein (i.e., 3 gm protein per 100 cal) and possess a NPC:N_2 ratio of 183, much higher than what is reported in the recent studies demonstrating benefit of protein repletion in critically ill children. Some centers add protein supplements to the tube feedings of all critically ill children who are receiving standard pediatric products.

Standard pediatric tube feeding formulas contain relatively low amounts of protein and are often supplemented with additional protein.

5.10.1 Enteral Formulas: Modified

Patients with macronutrient malabsorption, either anticipated or documented, may require a formula with contents altered to circumvent the deficiency. In patients with known pancreatic insufficiency (e.g., cystic fibrosis, pancreatitis), formulas that contain peptide and medium-chain triglycerides to bypass the pancreatic enzymes trypsin and lipase may be better tolerated in the acute setting. A continuum of levels of protein hydrolysis from large peptides to amino acids is available in the commercially available products and can be used in a variety of settings, such as protein intolerance (protein-losing enteropathy), protein allergy, and suspected gut atrophy. Patients with liver failure or cholestasis may require a greater concentration of medium-chain triglycerides, which bypass the biliary/micellar fat absorption system. Similarly, patients with chylothorax or chylous ascites require a formula with low fat content and/or a high percentage of fat as medium-chain triglycerides. However, in the setting of fat intolerance, care must be taken to supply a minimum of essential fatty acids to prevent deficiency.

5.10.2 Enteral Formulas: Specialized

Specialized formulas for specific disease states have been created and are commercially available. Specifically, nutritional supplements for patients with renal failure exist which are low in protein, high in caloric density, and with vitamin and mineral profiles, which complement the needs of the patient in renal failure whether or not they need dialysis. However, current SCCM/ASPEN guidelines for adults recommend not to restrict protein intake in the presence of acute kidney injury. For diabetics and critically ill patients who have problems with glycemic control, there are formulas, which are low in carbohydrate and higher in fat, with a formulation that optimizes the glycemic response. For patients with chronic pulmonary disease, cystic fibrosis, or acute respiratory distress syndrome, there are formulas which provide a high fat content and, therefore, provide a favorable RQ to decrease carbon dioxide retention. More rarely, patients with intestinal brush border enzyme deficiencies and inborn errors of metabolism will require highly specialized elimination formulas and should be referred to a dietitian and appropriate medical specialists.

5.10.3 Probiotics

The use of probiotics has gained a great deal of favor among pediatricians, who use these products to ameliorate the changes in gut microbiome in patients under treatment with antibiotics. The use of probiotics in the PICU has similarly gained favor. One study showed that in septic patients, the use of probiotics correlated with decreased pro-inflammatory cytokines and increased anti-inflammatory cytokines. While there have been other studies showing that the use of probiotics offers advantages to certain critically ill children by reducing nosocomial diarrhea and treating acute gastroenteritis, expert opinion suggests that it should not be employed broadly, and caution is indicated particularly for immunocompromised patients and those with central venous lines (related to specific components of some products).

5.10.4 Parenteral Nutrition

Frequent monitoring of serum electrolytes is necessary in patients receiving total parenteral nutrition.

For patients who cannot receive adequate enteral nutrition, parenteral nutrition is considered a safe and effective alternative. A great many variables must be assessed in preparing the parenteral nutrition formulation to assure that the correct amounts of electrolytes and calories are administered in the appropriate fluid volume. The process of ordering parenteral nutrition begins with determining the fluid needs of the child. Next, the number of calories to be supplied from lipid and dextrose is determined. Glucose delivery should not exceed 6 mg/kg/min in younger children or 4 mg/kg/min in older children and adults, although actual thresholds should be guided by frequent measurements of serum glucose levels. Care should be taken in prescribing pro-inflammatory soy-based intravenous fat emulsion (IVFE) in critically ill children with systemic inflammation. While there is no specific pediatric data, the evidence of harm from adult studies is compelling. When using IVFE during the later stages of critical illness, monitoring of serum triglyceride levels is essential because hypertriglyceridemia may occur and elevated serum triglyceride levels are a contraindication to the use of lipids in parenteral nutrition. Protein needs,

usually ranging from 1 gram per kilogram in highly protein-restricted patients to 3.0 grams per kilogram in neonates or older pediatric patients with severe nitrogen loss, can be satisfied with standard amino acid formulas. However, latest SCCM/ASPEN guidelines for critically ill adults recommend against routine protein restriction in the presence of hepatic or renal failure. Data from the PEPaNIC trial suggests that late (after 7 days) initiation of parenteral nutrition is advantageous over starting on day one of admission. However, the feeding protocol followed by this group provided early soy-based IVFE in quantities greater than the amount of protein intake, an approach well outside SCCM/ASPEN recommendations for adults. Indeed, this is the same group that has been criticized for their overfeeding with TPN in the adult tight glucose control studies. Current SCCM/ASPEN guidelines for adults recommend against soy-based IVFE for the first 7 days of TPN, regardless of when TPN is started in the critical illness. The availability of alternative IVFE products with fat sources, including olive oil, fish oil, and medium-chain triglycerides, is likely to change the approach to timing of IVFE use and help in the prevention of essential fatty acid deficiency. One such product has been successfully used in some pediatric populations. Vitamins and trace minerals should be added daily with additional selenium, zinc, and other vitamins as needed for specific clinical scenarios. The assistance of dietitians, pharmacists, and other nutrition experts is helpful in developing the appropriate formulation of calories, electrolytes, and minerals. Daily laboratory evaluations must be performed to guide the appropriate administration of electrolytes including calcium, phosphorus, and magnesium and glucose.

5.11 Summary

Critically ill children in the PICU pose a challenge on many levels. The determination of nutritional needs and the provision of appropriate calories, protein, and other nutrients are essential for wound healing and recovery from critical illness. Despite a general paucity of literature specific to pediatric critical care, the preponderance of available studies and opinion as well as information extrapolated from the adult literature emphasizes the importance of adequate nutrition for these vulnerable patients and the risks of malnutrition. The wide variety of disease states, the high level of acuity, and the ever-changing clinical status of the PICU population provide a challenge for practitioners to provide the appropriate nutrition to each individual patient.

Review Questions

1. A 7-year-old male is admitted to the pediatric intensive care unit with respiratory failure secondary to severe restrictive lung disease. He requires intubation and mechanical ventilation. Despite multiple interventions, he continues to have severe hypercarbia that has been fairly well compensated for by his kidneys. Which of the following feeding regimens should be avoided in this child?
   A. One with a relatively high carbohydrate content
   B. One with a relatively high fat content
   C. One with a relatively high multivitamin content
   D. One with a relatively high protein content
   E. One with a relatively high sodium content

2. Which of the following vitamins/minerals contributes to the biochemical functions of collagen formation, biosynthesis of bile, and catecholamines and demonstrates antioxidant properties?
   A. Selenium
   B. Vitamin B12
   C. Vitamin C
   D. Vitamin E
   E. Zinc

3. A 9-year-old female with acute myelogenous leukemia has been admitted to the pediatric intensive care unit for a week with alpha-streptococcal sepsis. The child is neutropenic recovering from myelosuppressive chemotherapy. She has no other organ system failures with adequate renal and hepatic function. Her only medications include antimicrobials, granulocyte colony-stimulating factor, and a proton pump inhibitor. Which of the following markers of adequacy of nutrition would be most helpful in assessing the acute nutritional state of this critically ill child?
   A. Serum albumin concentration
   B. Serum ferritin concentration
   C. Serum prealbumin concentration
   D. Serum transferrin concentration
   E. Total lymphocyte count

4. Which of the following has been associated with fatty infiltration of the liver, increased metabolic stress, and pulmonary compromise characterized by difficulty in weaning from the ventilator as the result of an unfavorable respiratory quotient?
   A. Continuous jejunal feedings
   B. Essential fatty acid deficiency
   C. Overfeeding
   D. Protein malnutrition
   E. Total parenteral nutrition

5. Which of the following conditions would represent a contraindication to enteral feedings?
   A. Acute respiratory distress syndrome
   B. Gastroesophageal reflux disease
   C. Infantile coarctation of the aorta
   D. The use of extracorporeal membrane oxygenation
   E. Traumatic brain injury

6. A 4-month-old develops a persistent left-sided pleural effusion. Thoracentesis reveals a milky-colored fluid with a high concentration of lymphocytes and triglycerides. Which of the following nutritional plans would be most appropriate for this infant?
   A. A diet high in fat
   B. A diet low in fat
   C. A diet high in protein
   D. A diet low in protein
   E. A diet with a normal balance of carbohydrate, fat, and protein

7. A typical standard enteral formula for healthy infants and children contains approximately what percentage of calories from carbohydrates?
   A. 30%
   B. 40%

C. 50%
D. 60%
E. 70%

8. In beginning total parenteral nutrition in a critically ill infant, a reasonable initial glucose infusion rate would be which one of the following?
   A. 5 mg/kg/min
   B. 10 mg/kg/min
   C. 15 mg/kg/min
   D. 20 mg/kg/min
   E. 25 mg/kg/min

9. Which of the following statements is false about nutrition support during adult or pediatric critical illness?
   A. The largest multicenter study of tight glucose control in pediatric critical illness demonstrated no benefit of tight glucose control.
   B. The most recent SCCM/ASPEN guidelines for adults recommend protein restriction with critical illness acute kidney injury in order to prevent significant increase in BUN.
   C. Calorie prescription for critically ill children based on standard equations results in frequent caloric overfeeding.
   D. The limited evidence available from study of enteral feeding in critically ill children is consistent with SCCM/ASPEN guidelines for adults with regard to emphasis on protein.
   E. Current SCCM/ASPEN guidelines for adults recommend against soy-based IVFE for the first 7 days of TPN, regardless of when TPN is started in the critical illness.

10. A 14-year-old male was admitted 10 days ago following motor vehicle accident during which he sustained closed traumatic brain injury, pulmonary contusion, liver laceration, and femur fracture. He is recovering from his injuries with discontinuation of ICP monitoring, improved neurological exam, and no signs of infection. Enteral feedings were initiated on day 4. To provide more protein than available in the standard pediatric product, he was placed on the adult formulation which provides 4 gm protein per 100 calories. What is the NPC:N_2 ratio of his tube feeding regimen?
    A. 89
    B. 156
    C. 183
    D. 131
    E. 250

Answers

1. A
2. C
3. C
4. C
5. C
6. B
7. C
8. A
9. B
10. D

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Pharmacology

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Contents

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6

Learning Objectives

- Differentiate between the concepts of pharmacokinetics, pharmacodynamics, and pharmaceutics
- Describe basic pharmacokinetic constructs and identify variability for each in critically ill pediatric patients, including:
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- Compare and contrast first- and zero-order elimination kinetics
- Describe the effects that organ dysfunction may have on the kinetics of drug disposition
- Identify pharmacokinetic challenges related to the use of extracorporeal membrane oxygenation in critically ill pediatric patients
- Summarize the pharmacokinetic parameters that influence the disposition of drugs in patients undergoing continuous renal replacement therapy
- List drugs and/or drug classes that exhibit variable pharmacokinetic parameters in the obese pediatric patient
- Summarize the impact of therapeutic hypothermia on the pharmacokinetic profile of medications commonly used in critically ill pediatric patients
- Explain how pharmaceutical factors influence medication pharmacokinetics and pharmacodynamics

6.1 Introduction

Pharmacokinetics is the science of how the body acts on a drug, while pharmacodynamics is the study of how a drug acts on the body or microorganism.

Pharmacology is the study of exogenous chemicals and their actions within the body. The science of pharmacology encompasses pharmacokinetics, pharmacodynamics, and pharmaceutics. Pharmacokinetics involves understanding the movement of a pharmacologic substance throughout the body. By studying a drug's pharmacokinetics, one can understand what the body does to the drug. Pharmacodynamics describes the effects of a drug and its mechanism of action on a body or infecting microorganism. Pharmaceutics is the science of pharmaceutical systems that focuses on drug preparation and dosage forms. An understanding of the effects of both age and illness on drug kinetics and dynamics is crucial to the practice of pediatric critical care.

6.2 Pharmacokinetics

ADME stands for **a**bsorption, **d**istribution, **m**etabolism, and **e**limination; this acronym represents a standard organization for describing a drug's pharmacokinetic properties.

Pharmacokinetics (PK) deals with the processes of absorption, distribution, metabolism, and elimination (ADME). Once a drug is administered, it must then be absorbed through cell membranes and distributed into different compartments in the body. The drug may be metabolized at various stages of absorption, with the most common site of metabolism being the liver. Many drugs are inactivated by these metabolic processes, while others are transformed and/or activated into molecules with additional activity. Elimination describes how and where a drug (or its metabolite) is removed from the body. The collective ADME processes represent a standard method for describing the pharmacokinetics of any drug.

A drug's pharmacokinetics may be analyzed by compartmental or physiologic models. **Compartmental pharmacokinetics** utilizes mathematical models to describe drug distribution. Using these models, it is assumed that after a drug is absorbed it is distributed into a system of connecting compartments

that are not anatomically based; the rate of transfer into and out of each compartment is represented by a constant, k. A drug may distribute according to a single compartment or a multi-compartment model (Fig. 6.1).

Single compartment pharmacokinetic models assume a drug achieves instantaneous distribution and equilibration throughout all the body's tissues. It is important to appreciate that this model does not imply the concentration of the drug will be equal throughout the body but rather that changes in the plasma concentration of the drug will result in a proportional change in all tissues. A multi-compartment model describes the concentrations of a drug in different tissue compartments as determined by rate constants that are specific to the interface between two given compartments. In a multi-compartment model, the plasma (bloodstream) is typically considered to be the central compartment. An example of a drug that distributes in the body according to a three-compartment model is the general anesthetic propofol. After intravenous (IV) administration directly into the bloodstream, propofol rapidly distributes into the central nervous system (CNS) where it exerts its anesthetic effects; however, it also distributes more slowly into the peripheral tissues which may become saturated during prolonged infusions (Fig. 6.2). The rapid rate of transfer from the plasma (compartment 1) to the CNS (compartment 2) is defined by the rate constant, k_{12}. The slower rate of transfer to the peripheral tissues (compartment 3) is described by k_{13}. Propofol may also distribute from the CNS and peripheral tissues back into the plasma, defined by the rate constants k_{21} and k_{31}, respectively. In compartmental PK models, if two given tissue beds have similar transfer rates and concentration profiles, they may be considered a single compartment for simplification. Elimination from the central compartment may occur via a variety of mechanisms and is defined by a given elimination rate constant, k_e.

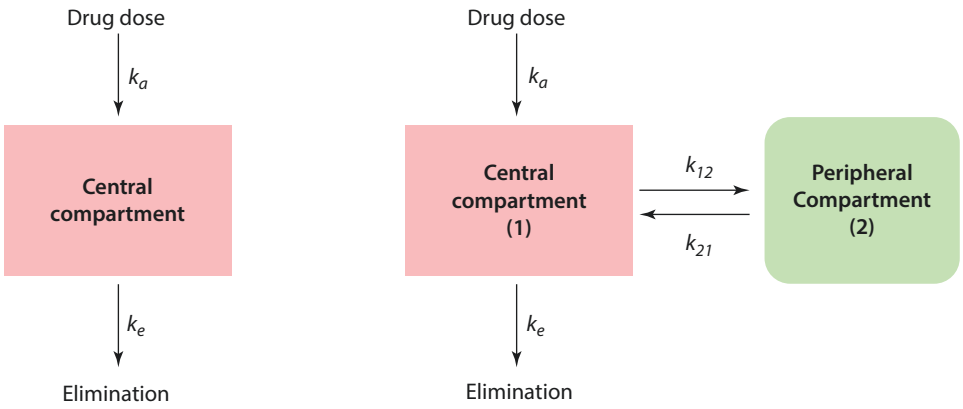


Fig. 6.1 One- and two-compartment pharmacokinetic models

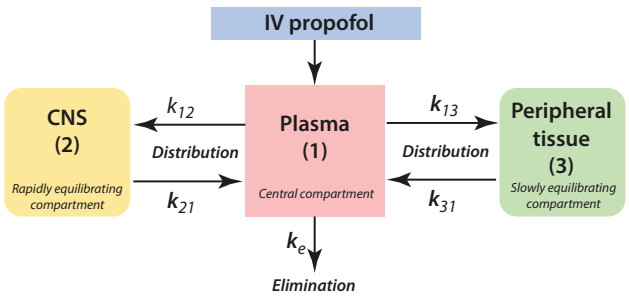


Fig. 6.2 A three-compartment pharmacokinetic model describing the distribution and elimination of propofol

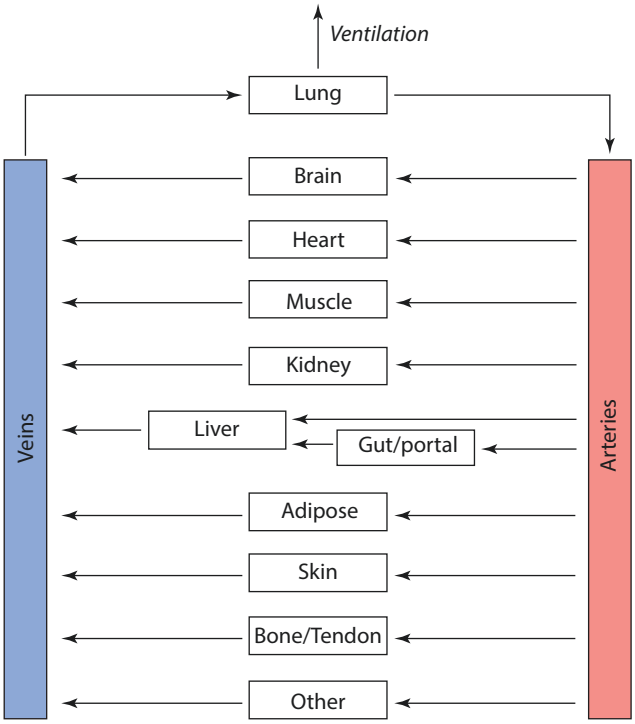


Fig. 6.3 Perfusion-based physiologic pharmacokinetic model

Vessel-rich organs such as the brain, kidney, lung, and heart may experience medication effects more rapidly than vessel-poor regions (e.g., adipose tissue), which may experience a delay in therapeutic concentration attainment.

In contrast to compartmental models, **physiologic models** use known physiologic and biochemical data to describe the distribution of medications throughout organ systems. These models separate the body into anatomically relevant compartments of defined volumes and perfusions that are connected in anatomical order (Fig. 6.3). Drug entry into each organ is based on the drug's partition coefficient and the organ's relative perfusion. "Vessel-rich" organs (e.g., brain, kidney, lungs, heart) may experience medication effects more rapidly, while "vessel-poor" regions (e.g., adipose tissue) may experience a delay in obtaining therapeutic drug concentration due to lower relative perfusion. Over time, vessel-poor tissues may serve as slowly filling depots for certain drugs. An example of this is the lipophilic drug diazepam. After initial administration of a single dose, CNS effects are seen relatively quickly due to the high degree of brain perfusion. Following early distribution to the brain, there is secondary redistribution to muscle and adipose tissue. With repeated or prolonged administration of diazepam, muscle and adipose tissue become a large drug reservoir that provides a source for continued action of the drug long after discontinuation.

Although compartment- and physiologic-based pharmacokinetic models may provide valuable theoretical information about a drug's behavior in the body, clinical applicability may be limited by the multiple assumptions made by each model. Regardless of which model is used, understanding fundamental pharmacokinetic concepts is required to appreciate how a drug moves throughout the body after administration.

6.3 Absorption

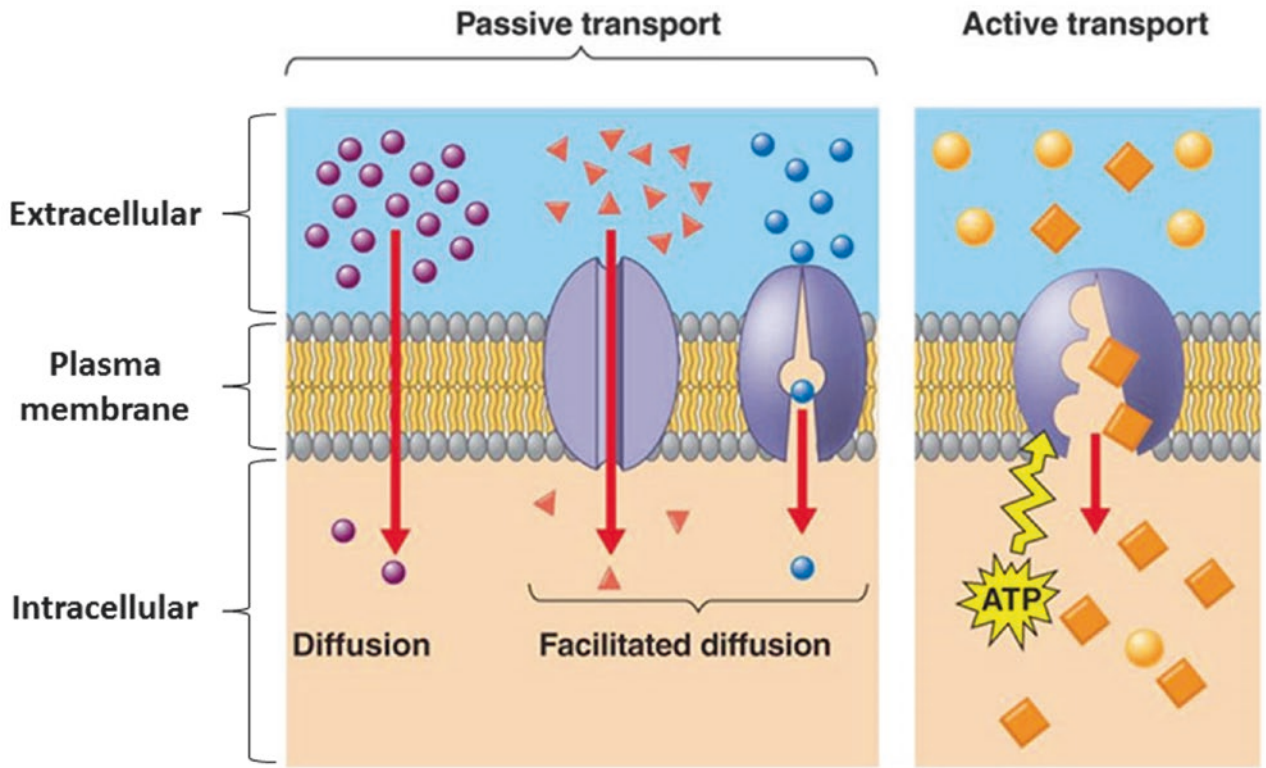
Absorption is the movement of a drug from its site of administration to the bloodstream. The route of administration may be categorized broadly as either **enteral**, if the drug is delivered via the alimentary tract, or **parenteral**, if any site outside the gastrointestinal tract is utilized.

A basic understanding of the cellular **plasma membrane** is essential when describing the processes involved in drug absorption. The plasma membrane consists of a phospholipid bilayer that is amphipathic (i.e., having both hydrophilic and hydrophobic regions; ◘ Fig. 6.4). This bilayer represents a barrier that prevents ions, proteins, and other molecules from moving into or out of the cell. The hydrophobic hydrocarbon chains are oriented inward; the polar, hydrophilic heads are oriented outward. Proteins and lipid molecules are embedded within the lipid bilayer and form the basis for various ion channels, receptors, and transporters. Most drug molecules can move across the cell membrane by passive diffusion, facilitated diffusion, or active transport.

Drugs may move across the cell membrane by passive diffusion, facilitated diffusion, or active transport.

Passive diffusion involves a molecule moving through the lipid bilayer, down its concentration gradient, and is dependent on the molecule being lipid soluble. **Facilitated diffusion** is also a passive process that relies on an electrochemical and/or concentration gradient and membrane proteins that form channels and transporters. Examples of substances transported into cells using facilitated diffusion include ions and glucose (when entering red blood cells). **Active transport** is an energy-dependent process that moves a substance against its electrochemical or concentration gradient. Primary active transport involves the hydrolysis of ATP to generate energy to move drugs or solutes across the plasma membrane (e.g., Na^+/K^+-ATPase pump), while secondary active transport utilizes an electrochemical gradient of one solute to move a second solute against its gradient (e.g., Na^+/Ca^{2+} antiporter). Most drugs are absorbed across the cell membrane by passive diffusion, although some substances (e.g., vita-

Most drugs are absorbed through the cell membrane by passive diffusion.



◘ **Fig. 6.4** Processes of drug movement across the plasma membrane. (Reece JB, Urry LA, Cain ML, Wasserman SA, Minorsky PV, Jackson RB. *Campbell's Biology*, 9th ed, ©2011. Reprinted with permission of Pearson Education, Inc., New York, NY)

mins, glucose, amino acids) are absorbed by active transport mechanisms. Multiple factors affect the rate and degree of drug absorption in a normal, healthy patient; critical illness may alter the absorption kinetics even more unpredictably depending on the type and severity of illness.

Bioavailability (F) describes the fraction of an administered drug dose that reaches the systemic circulation (central compartment). A drug administered enterally must first be absorbed from the gastrointestinal tract (stomach, intestine, etc.), and the final amount of drug delivered to the systemic circulation may be reduced by absorption kinetics and/or subsequent hepatic metabolism after it travels through the portal circulation.

$$F = \frac{\text{Amount of drug reaching the systemic circulation}}{\text{Dose of drug administered}}$$

where $0 < F \leq 1$

6

A drug administered intravenously should have 100% bioavailability.

A number of factors can influence the bioavailability of a medication including salt forms, first pass effect, pharmaceutical formulation, physiochemical properties, and patient-specific parameters. Due to direct delivery of the drug into the systemic circulation, intravenous administration usually results in 100% bioavailability ($F = 1$) unless extravasation occurs. Consider the following example:

» The bioavailability of intravenous (IV) ciprofloxacin is 100% (F = 1); therefore, a 400 mg IV dose results in 400 mg of ciprofloxacin being delivered to the systemic circulation (central compartment). The bioavailability of **oral** ciprofloxacin is only 80% (F = 0.8); therefore, in order to attain a similar serum concentration, a higher dose should be utilized. In this case, a 500 mg oral dose would be required in order to deliver 400 mg to the systemic circulation.

Following enteral administration, absorption of medications can occur at different sites along the gastrointestinal tract, including **oral**, **buccal**, **sublingual**, **gastric**, **jejunal**, and **rectal**. Most drugs are absorbed by passive diffusion, with lipid-soluble drugs moving across cell membranes and water-soluble drugs moving through aqueous channels. Drugs that resemble endogenous compounds (e.g., vitamins) require active transport to be absorbed. **Gastric pH** may affect enteral drug absorption significantly. Typically, weak acids are better absorbed from the stomach (pH 1.5–3.5) than the small intestine (pH 6–8) with the opposite being true for weak bases. Acid-labile compounds such as penicillin and pancreatic enzymes are degraded under acidic conditions and may have decreased bioavailability after prolonged exposure to stomach acid. The administration of H_2 antagonists or proton pump inhibitors increases gastric pH and may alter the absorption kinetics of drugs such as iron and itraconazole. Due to its larger surface area, the rate of absorption in the small intestine is generally much higher than in the stomach. If a drug moves too quickly (diarrhea) or too slowly (delayed gastric emptying) through the intestines, the rate of absorption may be reduced.

Changing the dosage form of a drug without understanding the pharmacologic implications can lead to supra- or subtherapeutic concentrations.

Some medications are commercially available in different salt forms. The **salt factor (S)** is the fraction of the administered dose (in salt form) that is the active drug. For example, aminophylline is the ethylenediamine salt form of the bronchodilator theophylline. Aminophylline has a salt factor of 80% ($S = 0.8$); thus, 1000 mg aminophylline is equivalent to 800 mg theophylline. Salt factors may vary based on dosage forms of the same drug. Phenytoin is manufactured as a parenteral injection of phenytoin sodium (which contains 92% phenytoin, $S = 0.92$), a chewable tablet of phenytoin acid (100% phenytoin, $S = 1$), or a suspension of phenytoin acid (100% phenytoin, $S = 1$). Changing only the drug form without a full understanding of the pharmacoki-

netic properties of the drug could lead to supra- or subtherapeutic drug concentrations. Small changes in phenytoin doses can produce large changes in serum concentrations, as this medication displays Michaelis-Menten pharmacokinetics (discussed later in this chapter).

The following equation is useful in determining the effect of a medication's salt form on the bioavailability:

$$\text{Amount of drug reaching the systemic circulation} = (\text{Dose})(S)(F)$$

where,

- S = salt factor
- F = bioavailability

If aminophylline ethylenediamine is 80% active theophylline ($S = 0.8$) and has an oral bioavailability of 100% ($F = 1$), the amount of active drug reaching the central compartment (plasma) after administering a 100 mg dose of aminophylline elixir is:

$$(100\text{mg aminophylline})(0.8)(1) = 80\text{mg theophylline}$$

Drugs absorbed in the stomach and small intestine enter the portal circulation and travel to the liver where they may undergo **first-pass metabolism** by hepatic enzymes before moving into the systemic circulation. First-pass hepatic metabolism may reduce the systemic bioavailability of many enterally administered drugs. For example, oral propranolol is almost completely absorbed through the intestine but is highly metabolized during its initial transit through the liver resulting in a bioavailability of only 30–40%. Other drugs that experience significant first-pass effect include lidocaine, opioids, midazolam, and nitroglycerin. In addition to hepatic metabolism, intestinal wall enzymes may metabolize portions of a drug prior to the drug reaching the circulation and may even pump a fraction of the drug back into the intestinal lumen. Cyclosporine, a calcineurin inhibitor used as an immunosuppressant after organ transplantation and to treat some autoimmune diseases, is an example of a drug metabolized by both the liver and the gut. Intestinal cytochrome p450 enzymes and p-glycoproteins may account for up to 50% of oral cyclosporine metabolism. Other enteral routes, such as sublingual or rectal, may bypass the portal circulation completely or partially. Venous drainage of the mouth to the superior vena cava bypasses the liver; thus, sublingual or buccal administration allows for direct absorption into the systemic circulation. The rectum is only partially drained by the portal circulation, and up to 50% of a drug absorbed rectally may bypass the liver completely. Drugs that undergo extensive first-pass metabolism may need to be given parenterally, sublingually, or in higher oral doses to achieve the desired effect. Conversely, some prodrugs require activation via hepatic metabolism, and their activity may depend on the first-pass effect. Valacyclovir is an example of an orally administered prodrug used to treat herpes simplex infections. It is converted to the active drug, acyclovir, by first-pass intestinal and hepatic metabolism with a resulting bioavailability of about 55% ($F = 0.55$).

First-pass hepatic metabolism may significantly reduce the bioavailability of an enterally administered drug.

Some prodrugs require activation by hepatic metabolism.

Drugs can be absorbed from the gut only when in solution. All other pharmaceutical formulations (capsules, tablets, etc.) must be converted into solution before being absorbed enterally. The formulation of a medication affects the rate of absorption and the time interval until it becomes available to the systemic circulation (Fig. 6.5). These differences may or may not be clinically significant and must be considered when changing formulations. For example, the difference in absorption rate between digoxin elixir and tablets is significant, while the difference between phenobarbital elixir and tablets is likely insignificant.

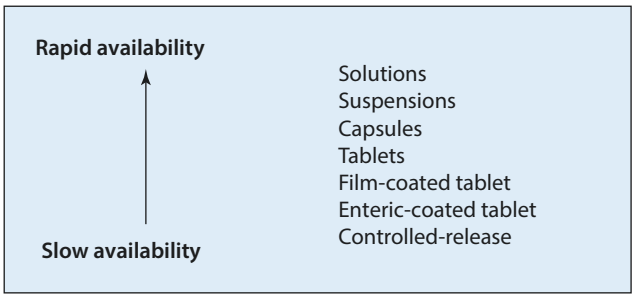


Fig. 6.5 Depiction of the continuum of rate of absorption of common enteral drug formulations

Once in solution, the solubility of the drug impacts its ability to be absorbed through the gut. Because of the electrochemical nature of the phospholipid bilayer, only lipid-soluble molecules (and some small molecules) passively diffuse through the cell membranes of the intestine. Ionized drugs are hydrophilic and therefore not well absorbed, preferring to stay in the aqueous medium of the gut lumen. As an example, vancomycin is a large, hydrophilic molecule resulting in very poor enteral absorption (its oral bioavailability is negligible in patients with healthy intestinal mucosa). For this reason, enteral vancomycin is utilized only to treat cases of bacterial enterocolitis where it may act locally on susceptible organisms (e.g., *Clostridium difficile* or *Staphylococcus aureus*).

Gastric emptying time can impact the rate and extent of enteral drug absorption.

Patient-specific parameters may also affect drug absorption. Depending on the drug, oral administration with food can increase, decrease, or have no effect on bioavailability. Delayed gastric emptying is often a complication of critical illness that may decrease the bioavailability of an intestinally absorbed drug. Decreased blood flow to the gastrointestinal tract can decrease enteral absorption, and patients with short bowel syndrome may have an impaired ability to absorb oral medications depending on which sections of bowel have been removed or are not functioning normally.

It is important to screen for intraluminal drug interactions in patients receiving enteral medications. Potential issues can be seen with fluoroquinolones, phenytoin, levothyroxine, and calcium, among others.

Drug interactions at the site of administration may also affect absorption. Drugs that slow gastric emptying may decrease the onset and/or rate of absorption of medications in the small intestine. Food components may also bind drug molecules, reducing their absorption through the gastrointestinal tract. Administration of phenytoin with enteral feeds results in **protein binding** that limits absorption. Levothyroxine may bind to fiber, calcium, iron, and even the feeding tube itself, thus reducing its bioavailability. Calcium compounds may act as chelators, binding to and decreasing enteral absorption of drugs such as ciprofloxacin. The chelation effect of calcium may also be utilized for therapeutic purposes: patients with chronic kidney disease may be prescribed oral calcium supplements to take both with meals to help prevent hyperphosphatemia (calcium acts as a phosphate binder) and on an empty stomach (to provide calcium supplementation).

Parenteral routes of administration refer to those outside the alimentary tract. As mentioned previously, **intravenous (IV)** administration has the benefit of complete bioavailability ($F = 1$) and rapid distribution. Irritating solutions may be delivered slowly or into a large, high-flowing vein in order to allow dilution by the blood. Some medications and/or concentrations should not be delivered into peripheral veins due to the risk of sclerosis or extravasation. Vasopressors or dextrose concentrations greater than 12.5% (12.5 g/100 mL) are preferably administered into large vessels via central venous catheters where they may be diluted by a larger volume of blood. The **intraosseous (IO)** route provides access to the systemic venous system comparable to the IV route. Care must be taken to ensure proper IO needle position within the bone marrow cavity, as significant extravasation and even acute compartment syndrome may occur with malpositioned needles. **Intra-arterial** administration is usually reserved for drugs with a targeted area of action, such as alteplase for arterial thromboses or che-

Parenteral administration is not limited to the IV route. Any site of administration outside the gastrointestinal tract is considered parenteral.

motherapy for certain solid-organ tumors. **Intramuscular (IM)** absorption of medications (e.g., epinephrine for anaphylactic shock) can be rapid but is dependent on blood flow to the muscles. Since fat is poorly perfused relative to muscle, muscle regions with higher adipose tissue content (such as the ventrogluteal region) are less preferred to the deltoid or vastus lateralis muscles. IM injections are limited by volume; thus, higher concentrations of certain medications may be required to deliver the required dose (e.g., IV ketamine 10 mg/mL vs. IM ketamine 100 mg/mL). **Subcutaneous (**formerly abbreviated **SC** or **SubQ)** injections also require smaller volumes and result in a slower, more sustained absorption of the drug due to less vascularity. **Topical** application is usually reserved for local activity (e.g., rashes, conjunctivitis), while **transdermal (TD)** patches are formulated for controlled release and systemic absorption of a drug. Transdermal absorption is dependent on the surface area of the patch, drug concentration, lipid solubility of the drug, use of an occlusive dressing, integrity of the skin, and temperature (damaged and/or higher temperature areas result in increased absorption). The **inhaled** route is a form of topical delivery that allows for both local activity in the lungs and some systemic absorption due to the large surface area of the pulmonary circulation. **Intranasal (IN)** delivery of sedatives/analgesics is increasingly used for procedural sedation due to the presence of dense capillary beds in the nasal mucosa that drain into the internal jugular vein, thus bypassing the liver and avoiding hepatic first-pass metabolism. The highly lipophilic nature of drugs such as fentanyl, midazolam, ketamine, and dexmedetomidine facilitates both transcellular absorption at the respiratory epithelium and penetration into the CNS. In intubated patients, the **endotracheal (ET)** route provides for limited absorption of certain lipid soluble drugs (lidocaine, epinephrine, atropine, and naloxone) in emergency situations where reliable IV/IO access cannot be established. Absorption through the alveolar capillary bed may result in substantially lower serum concentrations than achieved with IV administration and higher doses are usually recommended. **Intrathecal (IT)** administration of drugs is usually reserved for delivery of chemotherapy or antimicrobial drugs directly to the central nervous system. This route may be utilized to bypass the barriers between the blood, brain, and cerebrospinal fluid which often significantly limits the absorption of drugs.

The lipophilicity of drugs such as fentanyl, midazolam, ketamine, and dexmedetomidine facilitates both intranasal absorption and penetration into the CNS.

6.4 Distribution

Distribution is the reversible movement of a drug from the bloodstream to various sites in the body and is dependent on blood flow to a tissue bed, degree of plasma protein binding, capillary permeability, and lipophilicity of the drug. Once a drug has been administered and absorbed into the systemic circulation, it begins to distribute into peripheral tissues at rates governed by various rate constants (◘ Figs. 6.1 and 6.2). The rate of blood flow to a given tissue bed directly affects distribution to that compartment. Relative to tissue mass, the kidneys, heart, liver, and brain receive the highest blood flow, while the skeletal muscle, fat, and skin have much lower rates of blood flow.

The extent of **plasma protein binding** can impact drug disposition, including distribution and drug-drug interactions. To some degree, all drugs can bind to plasma proteins including albumin, α_1-acid glycoprotein, and lipoprotein. Albumin is a major carrier of acidic drugs, α_1-acid glycoprotein tends to bind basic compounds, and lipoproteins are known to bind several basic and neutral drugs. Reversible binding of drugs to plasma proteins affects the fraction of **free drug (i.e., active drug)**. Binding to plasma proteins is determined by the affinity of the drug for the protein, the availability of binding sites, and the plasma con-

centration of the drug. The extent of protein binding influences the rate and volume of distribution (discussed below). Drugs that are highly bound to plasma proteins may be displaced through competition with other compounds due to a finite number of sites available for binding free drug. This is the mechanism underlying several important drug interactions (e.g., sulfonamides and bilirubin, warfarin and phenytoin). Disease states such as hepatic or renal failure may reduce the availability of plasma proteins and thus decrease the extent of protein binding. If circulating plasma protein concentrations are lower than normal, the percentage of free drug increases. Even minor alterations in plasma protein binding may produce significant changes in therapeutic levels for highly bound drugs. For example, consider two hypothetical drugs ("A" and "B") that bind to a plasma protein ("X"). When drug A is administered alone, 99% binds to protein X, and the remaining 1% exists as free drug in the plasma. When drug B is introduced, it competes with drug A for binding sites on protein X and displaces an additional 1% of the total amount of drug A (Fig. 6.6).

For drugs that are highly protein bound, small changes in the degree of plasma protein binding may result in dramatic alterations in therapeutic drug levels.

The displacement of drug A from plasma protein X doubles the free fraction of drug A from 1% to 2%. This may also produce a doubling of therapeutic effect or, for drugs with a narrow therapeutic index (e.g., warfarin, phenytoin), a shift into the toxic range with potentially serious complications. When monitoring therapeutic concentrations of drugs such as phenytoin, it is crucial to distinguish between assays that report both total and free concentrations from those that report only the total serum concentration.

The **capillary permeability** of a drug is dependent upon the properties of the drug and structure of the capillary bed. **Lipophilic (hydrophobic) drugs** are generally lipid soluble, capable of dissolving into the capillary cell membranes without the aid of active transport mechanisms. **Hydrophilic drugs** are either charged or exhibit polarity and require either active transport mechanisms or slit junctions (fenestrations between capillary endothelial cells) to penetrate cellular barriers. The liver has capillary beds with large numbers of slit junctions through which small and/or ionized drugs may pass; in contrast, the capillaries of the CNS consist of endothelial cells with tight junctions that form the **blood-brain barrier** (Fig. 6.7).

Lipophilic drugs are able to dissolve through the cell membrane. Hydrophilic drugs require either active transport mechanisms or slit junction to penetrate cellular barriers.

Lipid-soluble drugs may pass directly through the cell membranes of the blood-brain barrier, while other drugs require specific transporters to facilitate entry into the CNS. Ionized drugs are generally unable to penetrate the endothelial cells of the blood-brain barrier due to the lack of slit junctions. A clinical example of this is the use of methylnaltrexone to treat opioid-induced constipation. The methylated form of naltrexone is a quaternary ammonium cation that cannot penetrate the blood-brain barrier, thus permitting peripheral opioid receptor antagonism without adversely affecting the CNS analgesic effects of any concurrently administered opioids (Fig. 6.8). While the blood-brain barrier is generally impermeable to hydrophilic drugs in healthy individuals, trauma or inflammatory disease states such as meningitis may alter the blood-brain barrier and increase its permeability.

After a drug reaches the plasma, the free (unbound) fraction may redistribute into other body compartments depending on the drug's size, structure, and

Fig. 6.6 The effect of protein binding and displacement on free drug levels

	Bound A (to protein X)	**Free A** (active)
Drug A (alone)	99%	1%
Drug A (with Drug B*)	98%	2%

**The presence of Drug B causes displacement of 1% of the total amount of Drug A from protein X*

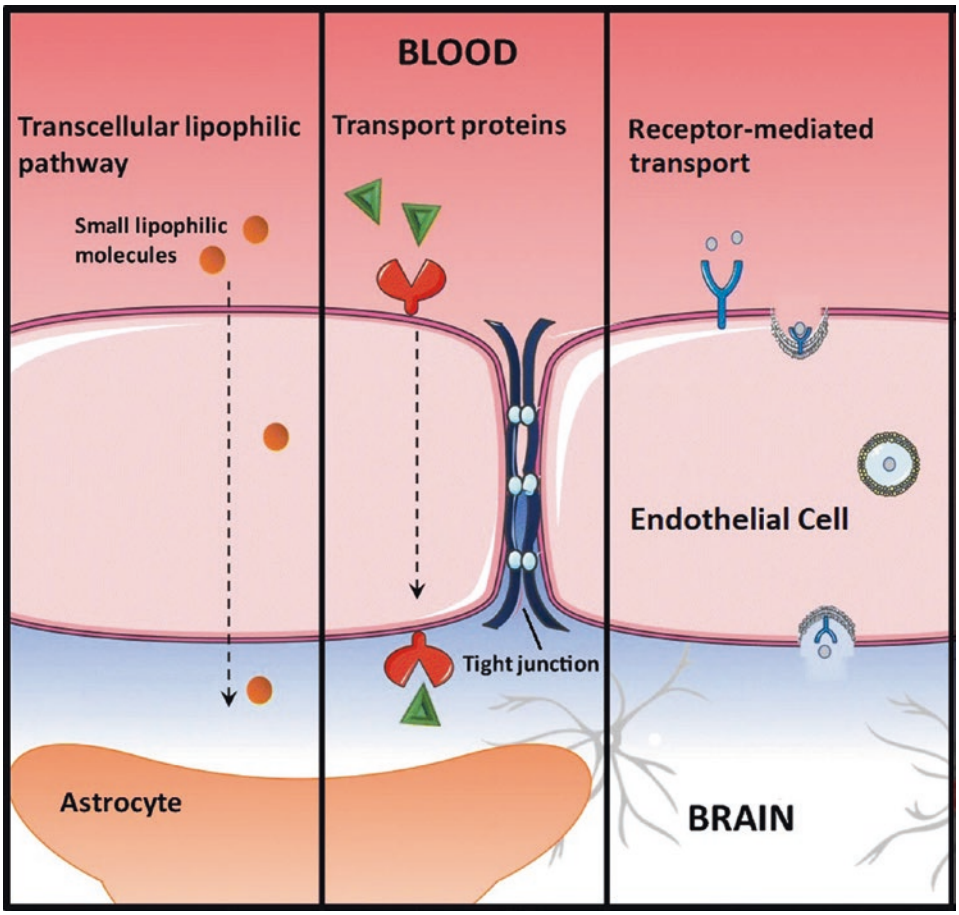
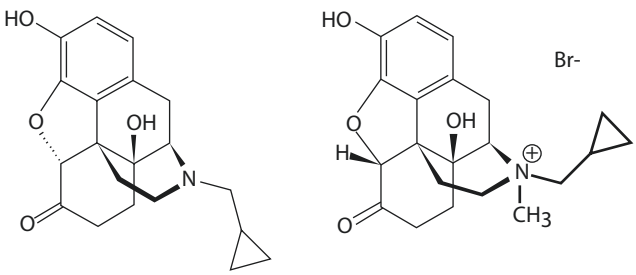


Fig. 6.7 The blood-brain barrier consists of endothelial cells bound together by tight junctions



Naltrexone

Methylnaltrexone
(as bromide salt)

Fig. 6.8 Methylation of naltrexone produces the quaternary cation methylnaltrexone which is unable to cross the blood-brain barrier

permeability. The **volume of distribution (V_d)** is a concept frequently used to describe a drug's distribution from the central compartment. V_d is not a true, measurable volume but rather a theoretical value indicating the fluid volume that would be required to contain the total amount of the drug in the body at the same concentration as measured in the plasma. V_d is dependent on the properties of the drug, including its lipid or water solubility and ability to distribute into different tissue compartments. V_d is defined by the following equation:

$$V_d = \frac{\text{Total amount of drug in the body}}{\text{Plasma concentration of drug}}$$

Volume of distribution is not a true, measurable volume; rather it is a theoretic value used to describe the extent of drug distribution to various tissues in the body.

Table 6.1 Drug characteristics affecting volume of distribution

Drug characteristics favoring large V_D	Drug characteristics favoring small V_D
Low molecular weight	High molecular weight
Low protein binding	High protein binding
High tissue binding	Low tissue binding
Increased membrane permeability	Decreased membrane permeability
Lipophilic	Hydrophilic
Uncharged	Ionized

Medications with a large V_d are widely distributed in the body, whereas those with a small V_d are mainly confined to the vascular space.

V_d is usually expressed in L/kg body weight. A large V_d indicates the drug is lipid soluble and/or highly concentrated into tissues, whereas a small V_d suggests the drug is more highly contained in the central compartment (plasma). An example of a medication with a small volume of distribution is warfarin. Because it is extensively bound to plasma proteins, warfarin has a V_d of 0.1–0.2 L/kg, indicating little of the drug is distributed beyond the vascular compartment. Conversely, amiodarone has a V_d of approximately 66 L/kg, resulting in tissue concentrations that are much higher than plasma concentrations.

Clinically, V_d is a useful parameter when calculating a **loading dose**. By rearranging the preceding equation, the following derivation is obtained:

$$\text{Loading dose} = V_d \times \text{Desired plasma concentration}$$

For example, if a phenobarbital level of 20 mcg/mL is desired for a neonate (population V_d = 1 L/kg), a 20 mg/kg load should be administered (20 mcg/mL • 1 L/kg = 20 mg/kg).

Knowledge of a drug's volume of distribution can guide decisions surrounding loading doses.

It is important to note that the volume of distribution is useful for initial loading and reloading doses, when calculating the amount of drug required to achieve a specific increase in plasma drug concentration starting from zero or from a known subtherapeutic concentration. These are often situations where one is "filling the tank." Volume of distribution alone is not useful for determining the frequency of maintenance or steady-state dosing. Factors that produce a small volume of distribution include those that prevent redistribution from the plasma to other tissue compartments such as low lipid solubility, high plasma protein binding, and decreased tissue binding (Table 6.1). Neonates inherently have a large V_d for most drugs due to a higher percentage of body water, lower levels of plasma proteins, and a relatively large liver and brain (highly perfused organs).

6.5 Metabolism

First-pass metabolism of an enterally administered drug may reduce the concentration reaching the systemic circulation. The liver and intestinal wall are the major sites of first-pass metabolism.

Drug metabolism includes all the processes that break down or transform drug molecules into inactive (or active) metabolites. Several organs and systems participate in drug metabolism, but the liver is the main site of metabolism for most drugs. A major function of the liver is to transform drugs via phase I and phase II reactions into water-soluble forms that can be excreted by the kidneys. Other sites of drug metabolism include the intestines, lungs, skin, plasma, and kidneys. **First-pass metabolism** of an enterally administered drug may reduce the concentration that reaches the systemic circulation. The liver and intestinal

wall are the major sites of first-pass metabolism. The amount of active drug molecules reaching the systemic circulation depends on the extent of metabolism in the liver and/or intestine.

Hepatic metabolism may include phase I and/or phase II reactions which transform the drug and enable it to be excreted by the kidney. **Phase I reactions** are *modification reactions* such as oxidation, reduction, hydrolysis, and cyclization/decyclization. These reactions serve to introduce reactive groups to the drug or to increase its polarity. Phase I reactions are frequently facilitated by the cytochrome p450 enzyme system located in the endoplasmic reticulum or inner mitochondrial membrane. If sufficiently polar, the metabolites may be ready for excretion after phase I reactions, otherwise they may undergo further metabolism via phase II reactions. **Phase II reactions** are *conjugation reactions* whereby the drug molecule is attached to polar or charged substrates such as a methyl group, acetyl group, glucuronic acid, sulfate, glutathione, or glycine group in order to enhance water solubility and renal elimination.

Phase I reactions modify a substrate to introduce reactive groups and/or increase its polarity. Phase II reactions conjugate a drug molecule with a polar or charged substrate, increasing its molecular weight and enhancing renal excretion.

A host of different cytochrome p450 enzymes act to oxidize or sometimes reduce drug and endogenous molecules. These enzymes are named in the following manner:

Isozyme: CYP3A4

CYP = cytochrome P450 enzyme
3 = family
A = subfamily
4 = individual member of the subfamily

Three families, CYP1, CYP2, and CYP3, are responsible for most drug transformations. CYP3A accounts for greater than 50% of phase I metabolism, predominantly via the CYP3A4 subtype. CYP3A4 is responsible for the metabolism of many drugs commonly utilized in the intensive care setting, including cyclosporine, methadone, acetaminophen, midazolam, diazepam, and tacrolimus.

CYP3A is one of the most important p450 isozymes, accounting for the majority of Phase I drug oxidation in the liver.

It is important to know which isozyme metabolizes a drug molecule to avoid clinically significant drug interactions which often result from the **induction** or **inhibition** of CYP enzymes (◘ Table 6.2). Information about the isozymes involved in the metabolism of a drug entity can be found in the drug's package insert, primary literature, or tertiary drug references. Additionally, many electronic medical records now include decision support software to alert ordering providers about potential drug-drug interactions.

An example of a potentially clinically significant drug interaction mediated by the p450 system is the interaction between midazolam and voriconazole. Midazolam is metabolized to a certain extent by CYP3A4, whereas voriconazole inhibits the action of CYP3A4. A patient receiving a midazolam infusion who is then started on voriconazole for a fungal infection may experience a clinically relevant increase in the concentration of circulating midazolam with potentially undesired effects.

Other tissues and systems that play considerable roles in drug metabolism include the gastrointestinal tract, lungs, skin, and kidneys. Lung tissue contains many CYP isozymes and other enzymes which participate in drug metabolism. For example, the inhaled steroid beclomethasone dipropionate is a prodrug which is metabolized to the active compound 17-beclomethasone monopropionate by lung esterases. In vitro studies of skin tissue have also demonstrated the presence of CYP isozymes and other drug-metabolizing enzymes. Topical propranolol, used to treat infantile hemangiomas, has been shown to undergo hydroxylation and dealkylation (phase I reactions) on skin biopsies. While the kidneys are routinely classified as organs of excretion or

Table 6.2 Cytochrome P450 drug interactions

Isozyme	Substrate	Inhibitors May cause accumulation of isozyme substrate	Inducers May enhance elimination of isozyme substrate
CYP3A4	Amiodarone Amlodipine Bosentan Buspirone Carbamazepine Cyclosporine Dexamethasone Diazepam Fentanyl Ketamine Lansoprazole Methadone Methylprednisolone Midazolam Nicardipine Ondansetron Pantoprazole Risperidone Sildenafil Tacrolimus Topiramate	Amiodarone Clarithromycin Cyclosporine Dexmedetomidine Erythromycin Fluconazole Fluvoxamine Grapefruit Isoniazid Ketoconazole Voriconazole	Barbiturates Carbamazepine Dexamethasone Fosphenytoin/ phenytoin Nafcillin Rifampin Vinblastine
CYP2D6	Amitriptyline Carvedilol Clonidine Codeine Dextromethorphan Flecainide Fluoxetine Haloperidol Hydrocodone Methadone Metoprolol Ondansetron Oxycodone Propranolol Risperidone Sertraline	Bupropion Clobazam Diphenhydramine Fluoxetine Haloperidol Paroxetine Quinidine Quinine	
CYP2C19	Citalopram Clobazam Diazepam Diphenhydramine Escitalopram Fosphenytoin/ phenytoin Labetalol Methadone Phenobarbital Voriconazole Warfarin	Cimetidine Fluconazole Fluoxetine Isoniazid Oxcarbazepine Voriconazole	Barbiturates Carbamazepine Fosphenytoin/ phenytoin Rifampin

Table 6.2 (continued)

Isozyme	Substrate	Inhibitors May cause accumulation of isozyme substrate	Inducers May enhance elimination of isozyme substrate
CYP2C9	Bosentan Carvedilol Fosphenytoin/phenytoin Ibuprofen Montelukast Naproxen Sildenafil Zolpidem	Amiodarone Fluconazole Metronidazole Miconazole TMP/SMX Valproic acid Voriconazole	Barbiturates Carbamazepine Fosphenytoin/phenytoin Rifampin
CYP1A2	Caffeine Diphenhydramine Flecainide Lidocaine Melatonin Olanzapine Ondansetron Warfarin	Cimetidine Ciprofloxacin Fluvoxamine	Barbiturates Carbamazepine Fosphenytoin/phenytoin Rifampin

Adapted from: *The Top 100 Drug Interactions: A Guide to Patient Management*, 2018

elimination, they also play an important role in the metabolism of drugs such as acetaminophen, furosemide, and morphine, which all undergo some degree of renal glucuronidation (a phase II reaction). The clinical significance of this metabolism has not been fully elucidated but should be taken into consideration in patients with renal insufficiency.

Non-organ-dependent metabolism is an important pharmacokinetic feature of several neuromuscular blocking and analgesic agents.

Non-organ-dependent metabolism of certain drugs by peripheral enzymes may also occur. Two non-depolarizing neuromuscular blocking agents, atracurium and cisatracurium, undergo peripheral metabolism known as Hoffman elimination (exhaustive methylation). Although this is not the exclusive mechanism of elimination (some drug undergoes renal clearance), it is an important factor to consider when choosing a neuromuscular blocking agent in the setting of renal or hepatic dysfunction. Succinylcholine is rapidly degraded by plasma cholinesterases, accounting for its short duration of activity. These enzymes are produced by the liver and are responsible for hydrolyzing succinylcholine to inactive metabolites. Plasma cholinesterase deficiency can result in prolonged neuromuscular blockade after succinylcholine administration and this deficiency can be inherited or acquired. An additional example of non-organ-dependent metabolism occurs with the short-acting analgesic remifentanil, which is rapidly metabolized by nonspecific plasma and tissue esterases.

6.6 Elimination

Renal elimination of drugs occurs primarily by passive glomerular filtration and active tubular secretion.

Drugs are removed from the body by many potential routes including the urine, bile, sweat, tears, or saliva. The two principal organs responsible for drug clearance are the kidneys and the liver. Renal elimination of medications is accomplished primarily by one of two mechanisms: passive glomerular filtra-

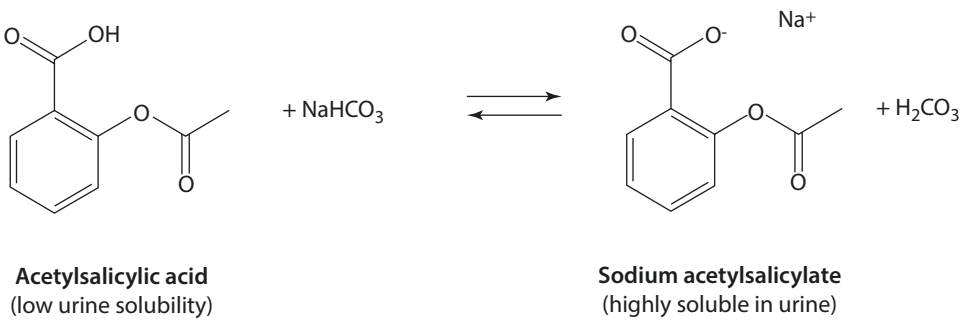


Fig. 6.9 Aspirin may be converted to its more soluble conjugate base (sodium acetylsalicylate) by the addition of sodium bicarbonate to IV fluids to alkalize the urine

tion or active tubular secretion. Most renal elimination is accomplished by passive **glomerular filtration**. Factors that determine the amount of drug filtered through the glomeruli include the size and charge of the drug, protein binding, and water solubility. Larger and more highly protein-bound drugs are not easily filtered, and anionic molecules are somewhat repelled by the negatively charged glomerular basement membrane. Estimations of glomerular filtration rate (GFR) commonly use 24-hour urine collection or estimation from serum creatinine measurement. In addition to filtration, drugs may be renally eliminated by **tubular secretion**. This is an active, energy-requiring elimination process occurring predominantly in the proximal tubule where active transport systems secrete organic acids and bases. Organic acids include most penicillins, cephalosporins, loop diuretics, thiazides, and nonsteroidal anti-inflammatory agents; organic bases include morphine and ranitidine. These drugs are secreted into the tubular fluid and then potentially reabsorbed at various sites in the nephron, depending on lipophilicity and urine pH. Alkalization of the urine may enhance renal elimination of weak acids such as aspirin via a process known as "ion trapping" (Fig. 6.9). Urine alkalization ionizes aspirin (acetylsalicylic acid, a weak acid with a pKa of 3.5) to its conjugate base, sodium acetylsalicylate, potentially increasing its elimination by enhancing urine solubility. The effectiveness of urine alkalization is debated, however, with some studies suggesting little to no benefit in enhancing urinary excretion of these substances.

Manipulation of urine pH may influence the elimination rate of certain drugs and metabolites.

Manipulation of urine pH also is used to modify the elimination rate of certain drugs and metabolites; for example, urine alkalization is used to limit methotrexate toxicity. Methotrexate demonstrates poor urine solubility at acidic pH, and its major metabolites, 7-OH-MTX and DAMPA, are six- to tenfold less soluble than the parent molecule, respectively. Increasing urine pH from 6.0 to 7.0 produces a five- to eightfold greater solubility of both methotrexate and its metabolites. These characteristics led to the recommendation for IV hydration containing 40–50 mEq sodium bicarbonate per liter of IV fluid prior to, during, and after the administration of high-dose methotrexate therapy.

The liver may also eliminate drugs via biliary excretion. After a drug is conjugated in the liver and excreted in bile, it may be reabsorbed via **enterohepatic recirculation** or eliminated in the feces. Medications that undergo biliary elimination include morphine, ceftriaxone, phenobarbital, and steroid and thyroid hormones.

6.6.1 Elimination Kinetics: First-Order vs. Zero-Order

When a drug is removed from the body as a *fixed percentage* of the remaining concentration over time, it is described as having **first-order elimination**. On a

linear plot, the decay curve will appear exponential (Fig. 6.10). First-order kinetics implies that the elimination mechanisms are not saturated. Since a fixed percentage of the drug is eliminated per unit time, a higher drug concentration should lead to a higher quantity eliminated over a specified time period. Because V_d and clearance are fixed in the setting of first-order kinetics, dose adjustments can be expected to produce proportional changes in serum concentration (e.g., doubling the gentamicin dose should double the serum concentration). Most drugs in use at therapeutic concentrations are eliminated via first-order kinetics.

Most drugs used clinically are eliminated via first-order kinetics.

Zero-order elimination occurs when a *fixed quantity* of drug (rather than percentage) is removed per unit time and the linear plot demonstrates linear decay. Zero-order kinetics implies a saturation of the elimination mechanisms. Many drugs exhibit first-order kinetics at therapeutic concentrations but then display zero-order elimination at higher concentrations when elimination pathways become saturated. Few drugs exhibit zero-order kinetics at therapeutic concentrations, one example being ethanol. Zero-order elimination may be seen in the setting of supra-therapeutic dosing or an overdose of some drugs. **Michaelis-Menten kinetics** describe the process of "saturable elimination" in which the rate of elimination approaches a maximum (V_{max}). Drugs that follow Michaelis-Menten kinetics will follow first-order elimination at lower serum levels, but as doses are increased and elimination mechanisms become saturated the rate of elimination approaches V_{max} and follows zero-order kinetics. When the rate of elimination is at V_{max}, further drug doses will lead to disproportionately elevated serum levels. This is especially important for drugs like phenytoin and fosphenytoin whose therapeutic serum levels are within the range of saturable elimination. Serum levels of these drugs should be monitored closely to ensure patients are not approaching toxic concentrations.

Many drugs exhibit first-order elimination kinetics at therapeutic dosing but then display zero-order kinetics at higher dosing when elimination mechanisms become saturated.

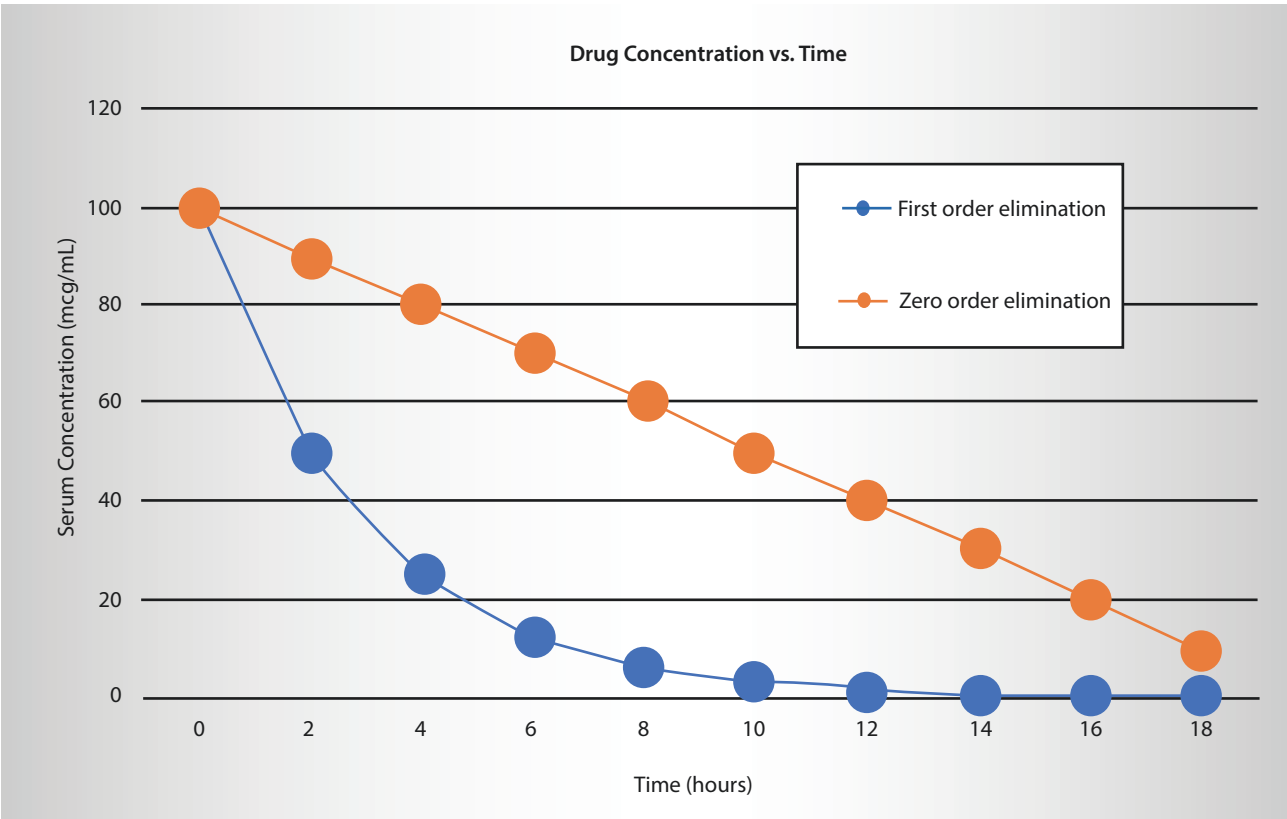


Fig. 6.10 Linear plot demonstrating first-order elimination (50% every two hours) vs. zero-order elimination (10 mcg/mL every two hours)

6.6.2 Half-Life and Steady-State

The elimination half-life is the amount of time required for the concentration of a drug to decrease by 50%.

The elimination **half-life ($t_{½}$)** is the amount of time required for the concentration of a drug in the body to decrease by 50%. Terminal half-life describes, more specifically, the time required for the plasma concentration of a drug to decrease by half. For example, gentamicin has a population half-life of approximately 2 hours in children. If the serum concentration of gentamicin was 10 mcg/mL after IV administration, the level 8 hours (four half-lives) later would fall to approximately 0.625 mcg/mL. Half-life is dependent on a drug's elimination constant (k_e), which can be determined from concentration-time plots. Drug half-lives reported in the literature are based on population variables and may be different in individual patients. The half-life of a drug in a particular patient may be affected by drug-drug interactions, genetic variables (rapid or slow metabolizers), organ dysfunction, etc. Assuming a drug has reached steady-state concentration, the half-life of a drug that follows first-order elimination can be calculated as follows:

$$t_{½} = \frac{0.693}{k_e}$$

Assuming consistent dosing, steady-state concentration is usually achieved after 4–5 half-lives of a drug have passed.

Related to half-life, **steady-state** concentration is reached when the amount of a drug entering the body is equal to the amount leaving the body. Assuming consistent dosing, steady-state concentration is usually achieved after 4–5 half-lives have passed (Fig. 6.11). In most clinical situations, it is important to ensure that steady-state concentrations have been achieved prior to making decisions about dosage adjustments to maintenance medication regimens. Loading doses for certain drugs (e.g., aminoglycosides, digoxin) may be used to achieve therapeutic serum concentrations more rapidly than waiting for 4–5 half-lives to pass.

Clearance (CL) is defined as the volume of plasma from which a substance is completely removed per unit time and is usually expressed as mL/min.

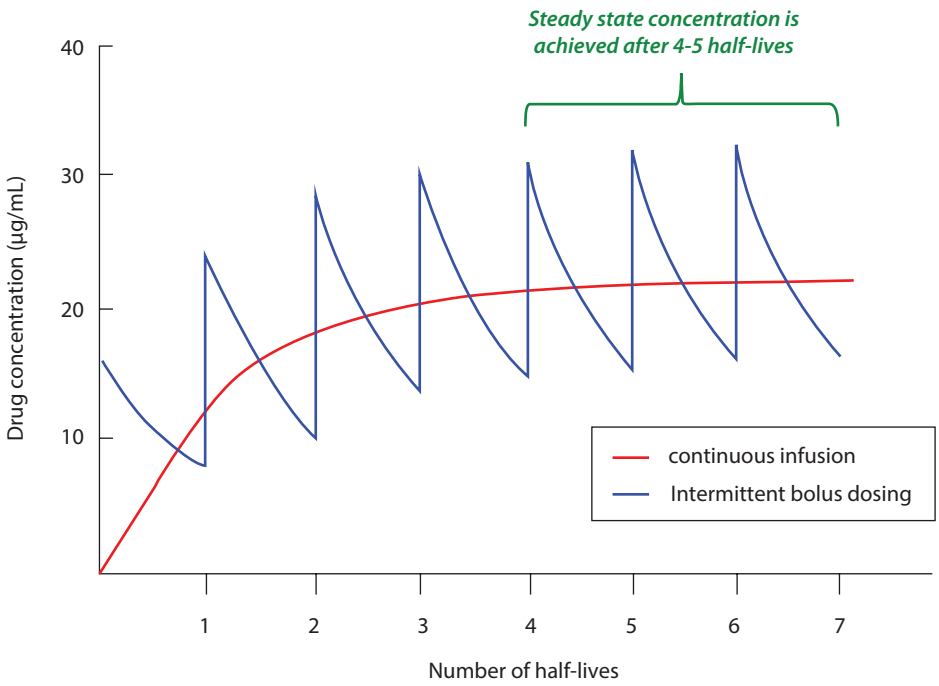


Fig. 6.11 Time to achieve steady state concentration of a drug. (Adapted from Australian Prescriber, 1996)

Clearance does not represent the amount of drug eliminated from the body; rather, it is the amount of plasma per unit of time from which the drug is cleared by the processes of metabolism and elimination. Mathematically, it is the product of the elimination constant and the apparent volume of distribution.

$$CL = k_e \times V_d$$

Clearance represents the fractional rate of drugs lost from the volume of distribution. The relationship between half-life and clearance can be understood by the equation below, in which k_e is equivalent to CL/V_d:

$$t_{½} = \frac{0.693 \times V_d}{CL}$$

Clearance represents the volume of plasma that is completely cleared of a drug by metabolism and elimination per unit time.

Of note, based on the equation above, drugs with a larger V_d will have longer terminal half-lives since more of the drug is distributed outside the central compartment. In the ICU setting, the relevance of this becomes apparent when short-acting drugs are administered as continuous infusions over prolonged periods of time. For example, the highly lipophilic drug propofol has a V_d of 5–10 L/kg in children. Bolus doses of propofol typically have a duration of action of 5–20 min; however, prolonged infusions lead to high concentrations of propofol in the peripheral tissues and a terminal half-life of up to 1–3 days. This accounts for the longer duration of action after discontinuation of prolonged propofol infusions.

Lastly, the total body clearance of a drug is the sum of individual organ clearances (hepatic, renal, other): $CL_{total} = CL_{hepatic} + CL_{renal} + CL_{other.}$

6.7 Pharmacodynamics

Pharmacodynamics describes the mechanism of action of a drug that produces physiologic and clinical effects. There are a myriad of mechanisms of action through which drugs exert their effects. Some drugs act directly without mediation by receptors. Examples include antacids that neutralize gastric secretions, cholesterol binding agents, and the osmotic diuretic mannitol. Receptor-mediated mechanisms are ubiquitous throughout human physiology and are the most extensively studied. A comprehensive discussion of these receptors and their mechanisms is beyond the scope of this chapter, but ◘ Table 6.3 provides a brief overview of commonly encountered physiological receptors and their pharmacodynamics related to drugs used in the ICU.

Pharmacodynamics may also describe how a drug acts on an infecting microorganism. The mechanisms of action of common antimicrobial agents are listed in ◘ Tables 6.4 and 6.5.

6.8 Pharmacokinetic and Pharmacodynamic Issues in the Pediatric ICU Setting

Many situations commonly encountered in the pediatric ICU have significant effects on pharmacotherapy. In particular, **organ failure** can have profound effects on both drug disposition and therapeutic response. In states of **fluid overload** such as **heart failure**, tissue injury with localized loss of capillary integrity, or generalized **capillary leak** from burn injury or sepsis, there may be significant expansion of the body's fluid compartments. This includes expansion of the extracellular fluid space with intravascular volume either increased or decreased. Fluid may accumulate in the third compartment (third space) such

Organ failure, fluid overload, and capillary leak all may contribute to the alteration of drug kinetics and require adjustments to drug dosing and/or frequency to ensure therapeutic levels.

Table 6.3 Physiologic drug receptors

Receptor type	Receptor example(s)	Drug example(s)[a]
G protein-coupled receptors are a large class of receptors formed by a single polypeptide chain with seven hydrophobic regions that represent transmembrane alpha-helices (also referred to as 7-TM receptors). The coupling of two G proteins occurs at the carboxy terminal within the cytoplasm, leading to downstream stimulation or inhibition of specific intracellular enzymes.	Adrenergic receptors ($ß_1$, $ß_2$, α_1) Opioid receptors	Epinephrine Dobutamine Norepinephrine Fentanyl, morphine
Enzyme-linked receptors have either intrinsic enzyme activity or are linked to cytosolic enzymes. These glycoproteins span the cell membrane only once and are activated through an extracellular receptor.	Tyrosine kinase	Imatinib
Nuclear receptors modulate gene expression. They are activated by lipophilic molecules that can diffuse across the plasma membrane and bind to intracellular nuclear receptors.	Steroid receptors Retinoic acid receptor Thyroid hormone receptor	Glucocorticoids ATRA T3, T4
Voltage-gated ion channels are involved in the regulation of cell membrane potential and the propagation of an action potential in excitable cells. They mediate Na^+, Ca^{2+}, K^+, and Cl^- conductance through membrane potential changes.	Na^+ channels Ca^{2+} channels	Lidocaine Phenytoin Nicardipine Gabapentin
Ligand-gated ion channels combine to form a binding site for neurotransmitters and an ion-conducting pore. These channels produce rapid changes in membrane permeability, modulating synaptic events in the nervous system.	GABA receptors NMDA receptor	Benzodiazepines Propofol Ketamine
Membrane transport proteins are integral transmembrane proteins involved in the transport of ions, proteins, or small molecules across the cell membrane. Two main types are *channels* and *carriers*.	Na-K-Cl cotransporter GLUT Gastric proton pump	Furosemide Glucose/dextrose Pantoprazole
Direct enzyme targets act upon one or more of the thousands of enzymes in the human body. Enzyme inhibition may be reversible or irreversible, depending on the reaction.	Phosphodiesterase Acetylcholinesterase Dihydrofolate reductase	Milrinone Neostigmine Methotrexate

[a]Drugs listed may be agonists/activators or antagonists/inactivators of a given receptor

as the pleural and peritoneal cavities. The net effect of the expansion of total body water in the critically ill is to increase the volume of distribution of all hydrophilic drugs that distribute widely throughout the body's water space. For example, the presence of significant edema and ascites may increase the V_d of highly water-soluble agents such as aminoglycoside antibiotics.

If a drug's dosing interval spans multiple half-lives, large peak-to-trough differences may occur and establishing adequate peak concentrations to ensure effectiveness may require significant increases in the individual dose. As a further consideration, if plasma clearance remains fixed but the size of the body's "tank" has markedly increased, half-life will increase because of the increase in

Table 6.4 Mechanisms of action for common antibacterial agents

Antibacterial sites of action				
Cell wall	**Ribosome/protein synthesis**	**DNA**	**Dihydrofolate reductase (DHFR)**	**Cell membrane**
Penicillins Cephalosporins Vancomycin Aztreonam	Macrolides Lincosamides Aminoglycosides Tetracyclines Rifampin Linezolid Quinupristin/dalfopristin	Metronidazole Fluoroquinolones	Trimethoprim/sulfamethoxazole	Daptomycin Colistin (polymyxin E)

Table 6.5 Mechanisms of action for common antifungal agents

Antifungal sites of action					
Cell membrane		**Cell wall**		**RNA/DNA**	
Azoles	Impair ergosterol synthesis	Echinocandins (Caspofungin)	Inhibit synthesis of beta (1,3)-D-glucan	Flucytosine	Disrupts protein and DNA synthesis
Amphotericin B	Binds to ergosterol causing membrane leakage				

V_d (recall that $t_{½} = 0.693 \times V_d/CL$). As a result, it may be required to increase the dosing interval to achieve adequate peak levels without elevated trough levels.

The function of the gastrointestinal system may have significant effects on drug kinetics and toxicity. **Delayed gut motility** may slow the peak response to enterally administered medications. Drugs that undergo extensive first-pass metabolism may have a significantly higher oral bioavailability in patients with **liver failure** than in patients with normal hepatic function. The capacity of the liver to metabolize drugs depends on hepatic blood flow and liver enzyme activity. Certain p450 enzymes are more susceptible than others to liver injury, which may lead to general or selective impairment of drug metabolism. Decreased liver synthetic function can result in hypoalbuminemia or decreased glycoprotein levels that may affect the protein binding of acidic or basic drugs, respectively, leading to an increase in free serum drug concentrations. Furthermore, medications that are normally highly protein bound may also have increased tissue distribution due to reduced plasma protein concentrations.

An understanding of the primary and alternate pathways of elimination for all medications is essential for the daily management of the critically ill child. **Renal failure** may alter the elimination of many drugs utilized in the ICU and medications with significant renal clearance require dose reduction. It is essential to understand whether a drug produces active or toxic metabolites that may accumulate in the setting of organ failure. For example, morphine is metabolized by the liver to an active metabolite (morphine-6-glucuronide) that is subsequently excreted by the kidney and should therefore be dose reduced or avoided altogether in renal failure. This may not be readily apparent to the clinician who knows that morphine is a hepatically metabolized drug. The emergence of renal protection strategies to mitigate or reverse the nephrotoxic

Clinicians should be aware of any active or toxic metabolites produced by a drug's metabolism, as these may accumulate in the setting of organ failure.

effects of medications has added another dimension to this issue. A growing body of literature demonstrates that augmentation of intrarenal blood flow may have a protective effect on renal function in the context of specific threats. For example, both theophylline and fenoldopam are intrarenal vasodilators that favorably affect renal function and augment diuresis in the presence of renal impairment (intrarenal vasoconstriction) caused by calcineurin inhibitors. Furthermore, a recent meta-analysis of the effects of theophylline on radiocontrast nephropathy demonstrated a protective effect of theophylline on renal function when combined with IV hydration.

The medication list of any critically ill patient should be reviewed and evaluated frequently based on changing patient status, organ function, and new drug-drug interaction.

An important part of daily patient care is the review of all medications in the context of any changes in patient condition, organ function, and new drug interactions. The critical care physician is challenged to manage the interplay between physiologic impairments of organ function and drug-related organ injury. The threats to renal and hepatic function posed by critical illness (e.g., shock, sepsis, etc.) must be balanced against the potential organ toxicity caused by potentially lifesaving drugs such as cyclosporine, vancomycin, amphotericin, aminoglycosides, and various other agents. Furthermore, the need to preserve adequate intravascular volume for optimizing organ perfusion must be balanced against the morbidity and mortality associated with generalized fluid overload.

Certain drugs used in critically ill patients may require dose adjustment in the setting of ECMO.

The use of **extracorporeal membrane oxygenation (ECMO)** is known to affect the pharmacokinetics and pharmacodynamics (PK-PD) of many drugs used in the ICU. For most infants and children, the ECMO circuit represents a significant expansion of circulating blood volume; hence, the volume of distribution (V_d) for many drugs increases. This increase in V_d has been demonstrated in vivo with drugs such as vancomycin and gentamicin. Individual components of the circuit also have the ability to increase V_d through drug **adsorption**. Highly lipophilic drugs such as fentanyl and midazolam may be adsorbed extensively by the polyvinyl chloride (PVC) tubing and oxygenator components. A 2012 study compared drug recovery from ECMO circuits with controls (PVC-lined glass jars) and found that up to 70% of fentanyl and 50% of midazolam were lost in the ECMO circuit during the first hour of therapy (Table 6.6). For this reason, a less lipophilic drug such as morphine may be a better analgesic for patients supported with ECMO. Drug clearance may also be impaired in patients requiring extracorporeal support; however, as patients requiring ECMO frequently have multi-organ failure, it is unclear to what degree clearance is affected by the circuit versus underlying organ dysfunction. Extensive PK-PD studies for many drugs are lacking in the pediatric population but small studies and case series suggest some cardiovascular drugs (esmo-

Fentanyl and midazolam demonstrated extensive binding (adsorption) to components of the extracorporeal membrane oxygenation (ECMO) circuit.

Table 6.6 Average drug recovery from ECMO circuits vs. controls, relative to baseline starting dose

	Drug recovery at 24 h	
	Control[a]	ECMO circuit
Fentanyl	82%	3%
Morphine	97%	103%
Midazolam	100%	13%
Vancomycin	99%	90%
Meropenem	42%	20%

[a]Polyvinyl chloride (PVC) jars with fresh human whole blood

lol, amiodarone, and sildenafil), diuretics (bumetanide), antimicrobials, and analgesics/sedatives may require dosing adjustments while on ECMO. Notably, the PK of inotropes and vasoactive agents such as dopamine and epinephrine appear to be less affected by extracorporeal circuits. In addition to the interaction between drugs and circuit components, the altered blood flow patterns seen in ECMO may affect organ function and drug kinetics. Some studies suggest the lack of pulsatile blood flow often observed in venoarterial (VA) ECMO may lead to microvascular changes and renal dysfunction, with further potential for impaired drug clearance.

Similar to ECMO, the use of **continuous renal replacement therapy (CRRT)** may also impact the PK-PD of certain drugs. The small pores of the CRRT membranes generally limit clearance to the unbound fraction of a drug. Thus, drugs that are more extensively protein bound are less likely to be cleared by the circuit; conversely, hypoproteinemia is often seen in critical illness and may result in increased clearance due to a higher free fraction of drug in the plasma. Drugs with higher V_d (lower proportion of drug in the intravascular space) will not be cleared as extensively. As with ECMO, the circuit itself may adsorb drugs resulting in a higher V_d and further reducing clearance. In addition to patient- and drug-specific factors, the mode of CRRT used, blood flow rate (Q_b), and dialysate flow rate (Q_d) may also affect the clearance of drugs during renal replacement therapy.

The small pores of the CRRT membrane generally limit drug clearance to the free (unbound) fraction of a drug.

Body composition plays a significant role in drug disposition in both healthy and critically ill children. **Pediatric obesity** is on the rise in the United States and has implications for medication dosing and management in the critically ill child. Current Centers for Disease Control and Prevention (CDC) statistics suggest 13.7 million children and adolescents (nearly 20% of the pediatric population) are considered obese, defined as a body mass index (BMI) ≥ 95th percentile for the child's age and gender. Having a larger relative proportion of adipose tissue can affect the distribution of many drugs, but the effect remains difficult to estimate with indirect measures such as BMI and body surface area (BSA). Different methods of drug dosing in children include weight-based, age-based, allometric scaling, and BSA-based dosing. Weight-based dosing is used most commonly, followed by BSA-based dosing, which is frequently utilized for dosing chemotherapy. BSA is commonly calculated using the Mosteller equation:

$$\mathrm{BSA}\left(\mathrm{m}^2\right) = \sqrt{\frac{\mathrm{height}\left(\mathrm{cm}\right) \times \mathrm{weight}\left(\mathrm{kg}\right)}{3600}}$$

Weight-based dosing strategies include using total body weight (TBW), ideal body weight (IBW), or adjusted body weight (ABW or IBW-Adj). While TBW is measured, IBW is calculated based on height and is used to limit the risk of overdosing in overweight patients. Several methods for calculating IBW in children have been reported, but currently no gold standard equation has been identified. The ABW (IBW-Adj) is a calculated weight frequently used by dieticians to estimate caloric requirements but also may be considered for dosing certain drugs when a child's actual weight exceeds 120% of his/her calculated IBW. It is important to consider the pharmacokinetic information available when dosing medications in obese children and the risk of under- or overdosing medications (◘ Table 6.7). Much of the data regarding weight-based dosing strategies for obese patients is obtained from adult studies, and, as such, consultation with a pediatric pharmacist should be considered whenever dosing questions arise.

For obese children, weight-based dosing recommendations may be based on total body weight (TBW), adjusted body weight (ABW), ideal body weight (IBW), or body surface area (BSA) since there is no gold standard method to adjust dosing in obese children.

Opioids such as fentanyl, hydromorphone, and morphine are primarily metabolized by the liver and eliminated either intact or as metabolites in urine.

Table 6.7 Weight-based dosing strategies for obese pediatric patients

	Calculation	Suggested use
Total body weight (TBW)	Measured	Cephalosporins heparin (loading dose) propofol succinylcholine vancomycin
Ideal body weight (IBW)	*Moore method:* (1) Using growth chart, plot height-for-age (2) Obtain percentile (3) Identify corresponding weight at the same percentile	Acyclovir cisatracurium digoxin levothyroxine midazolam (infusion) remifentanil rocuronium vecuronium
	McLaren method: (1) Using growth chart, plot height-for-age (2) Obtain percentile and draw horizontal line to 50th percentile (3) Draw vertical line to weight at the 50th percentile for the corresponding age	
	Body mass index (BMI) method: (1) Using BMI-for-age chart, obtain BMI at 50th percentile for patients age (2) Multiple by the square of the patient's height	
Adjusted body weight (ABW or IBW-Adj)	IBW + 0.4 (TBW – IBW) *For patients whose weight exceeds 20–30% of the IBW*	Amikacin cisatracurium enoxaparin gentamicin heparin (infusion) rocuronium/vecuronium tobramycin

Dosing of these medications depends on pharmacokinetic parameters of the drug and the drug's properties (lipophilic vs. hydrophilic). While recommendations support the use of ABW to dose hydromorphone and fentanyl due to their lipophilic properties and IBW when dosing morphine due to its hydrophilic properties, clinicians often start with IBW or TBW dosing and titrate upward toward a typical adult dose, as needed.

Since antimicrobial agents are generally hydrophilic, they carry the risk of being underdosed in obese children who have an increased V_d due to increased total body water. The penicillins and cephalosporins are typically dosed based on TBW up to the maximum adult dosing. Aminoglycosides are water soluble and are primarily eliminated by glomerular filtration. ABW should be used to dose gentamicin and tobramycin in critically ill, obese children, and appropriate therapeutic drug monitoring (TDM) should be undertaken to allow for appropriate dose adjustments. Vancomycin distributes into fluid and tissues widely and is eliminated by glomerular filtration. Some studies recommend dosing vancomycin in obese children based on TBW while using a maximum vancomycin in dose and adjusting based on trough levels.

Heparin and low molecular weight heparins (LMWH) are also affected by weight and body composition. Heparin is highly protein bound and is cleared primarily via macrophages and the reticuloendothelial system and to a lesser extent by the kidneys. Pharmacokinetic data suggest obese children should receive heparin bolus doses based on TBW, but infusion rates should be based on ABW due to the hydrophilic properties of the drug and the water content of adipose tissue. LMWH are primarily eliminated by the kidneys; for critically ill obese children, the dosing recommendation is to utilize ABW and titrate to target a desired anti-Xa activity level. As in all situations involving pediatric patients with a diagnosis of obesity, consultation with published dosing guidelines and/or a pediatric pharmacist is recommended.

Therapeutic hypothermia is occasionally utilized in the PICU to limit brain injury after cardiac arrest or to treat severe, refractory status epilepticus. The putative benefit of this therapy, specifically the limitation of secondary neurologic damage, may be impacted by the effects of hypothermia on drug disposition (ADME) and effectiveness. Human and animal studies demonstrate a complex relationship between hypothermia and drug metabolism, elimination, and response. Hypothermia reduces the function of the hepatic cytochrome p450 system, thereby decreasing the metabolism and clearance of drugs that interact with this enzyme family. For example, PK analysis demonstrates a >100-fold decrease in systemic clearance of midazolam when the subject's core temperature was lowered below 35°C, likely due to impaired CYP3A4 and CYP3A5 activity. Similar reductions in clearance during hypothermia are observed for other hepatically metabolized drugs including fentanyl, morphine, barbiturates, propofol, vecuronium, propranolol, phenytoin, and many others. Proposed mechanisms for hypothermia-induced reduction in activity of the p450 enzymes include reduction in the rate of redox reactions, decreased substrate affinity for enzymes, and changes in enzyme binding pocket conformation. In addition to impairing metabolism, hypothermia may also reduce the effectiveness of certain drugs. Morphine is hepatically metabolized by phase II glucuronidation reactions primarily to morphine-3-glucuronide (no analgesic effect) and morphine-6-glucuronide (reduced analgesic potency compared to the parent drug). Hepatic metabolism of morphine may be impaired by hypothermia; however, animal studies have shown that both morphine and its active metabolite have reduced affinity for the μ-opioid receptor as body temperature decreases, thereby reducing their potency. The net impact of hypothermia on morphine may be different for each patient, warranting close monitoring for both inadequate drug response and adverse effects.

Hypothermia may decrease the activity of hepatic cytochrome p450 enzymes by reducing the rate of redox reactions, decreasing substrate affinity for enzymes, and changing the enzyme binding pocket conformation.

6.9 Pharmaceutics

Pharmaceutics is the science of pharmaceutical systems and focuses on drug preparations and dosage forms. There are a number of important applications of pharmaceutics to the critically ill child such as the physicochemical properties of drugs, which should be considered when contemplating the site of administration. When administering parenteral preparations, knowledge of the formulation pH, concentration, and osmolarity is critical. Agents with a non-physiologic pH should not be administered intramuscularly as tissue necrosis can occur. Phenytoin, for example, is soluble only at a pH of approximately 11; therefore, intramuscular administration may cause local hemor-

rhagic necrosis and should be avoided. The administration of phenytoin through peripheral catheters or peripherally inserted central catheters should also be avoided due to the risks of phlebitis and precipitation, respectively. Fosphenytoin, the phosphorylated prodrug of phenytoin, has a pH of 8.6, allowing for safer IV and IM administration due to its more favorable pharmaceutical properties.

Concentration, pH, osmolarity, and vasoconstrictive properties may limit the safety of peripheral administration of some drugs.

In addition to pH, drug properties such as concentration, osmolarity, vasoconstrictive potential, or predisposition to induce phlebitis may limit the safety of peripheral IV administration. **Hyperosmolar solutions** may cause vascular endothelial damage and thrombophlebitis when administered in small blood vessels and these agents should be administered via a central venous catheter whenever possible. It is prudent to avoid prolonged peripheral administration of medications with an osmolarity >900–1100 mOsm/L. When information regarding the osmolarity of medications is not readily available, the clinician must rely on published maximum concentrations to guide the decision regarding administration route. Vasoconstrictive medications such as norepinephrine and phenylephrine may pose a higher risk of limb ischemia when administered peripherally. Medications inherently more likely to induce phlebitis when administered into small, peripheral veins include nafcillin, amphotericin B, propofol, and vancomycin. Management of tissue extravasation is agent specific and may include warm or cold compresses, elevation, or the use of an antidote such as hyaluronidase to promote dispersion from the site. Vasoconstrictive agents such as phenylephrine and norepinephrine can cause significant tissue necrosis if extravasation occurs; treatment may include local instillation of a vasodilator such as phentolamine. Consultation with a pharmacist and, if indicated, plastic surgery should not be delayed.

When administering multiple medications concomitantly through the same catheter, physical and chemical compatibility should be investigated prior to initiation. Multiple tertiary references and charts exist to assist with assessment of drug-drug compatibility. When utilizing these references, note the specific medication concentrations that were studied as only those concentrations listed may be extrapolated to clinical practice. For example, dobutamine 1 mg/mL is compatible with a dilute KCl solution (20 mEq/L) but incompatible with a concentrated KCl solution (160 mEq/L).

Preservatives and solubilizing agents may pose a higher risk of toxicity and injury in young children.

Attention should also be paid to the content of **preservatives** and **solubilizing agents** in medications used in critically ill children, particularly when high doses are used or in the setting of organ dysfunction. Benzalkonium chloride, a bactericidal preservative found in many albuterol nebulizer solutions, may produce bronchoconstriction in some patients. Benzyl alcohol is a preservative found in some injectable drugs which may accumulate, resulting in serious toxicities and even death. High exposure to benzyl alcohol-containing products in neonates has been associated with an increased incidence of metabolic acidosis, neurological impairment, cerebral palsy, and intraventricular hemorrhage. If possible, preservative-containing medications should be avoided in patients less than 60 days of age or in those with severe renal impairment. Propylene glycol is a solubilizing agent found in formulations of drugs such as pentobarbital, diazepam, and lorazepam and is normally metabolized by the liver to lactic acid (◘ Fig. 6.12). When administered at high doses over a sustained period of time (e.g., during a pentobarbital-induced coma), both propylene glycol and lactic acid may accumulate resulting in a hyperosmolar state with an increased anion gap acidosis. Renal dysfunction may also exacerbate this state as the excretion of unchanged propylene glycol is impaired. Certain

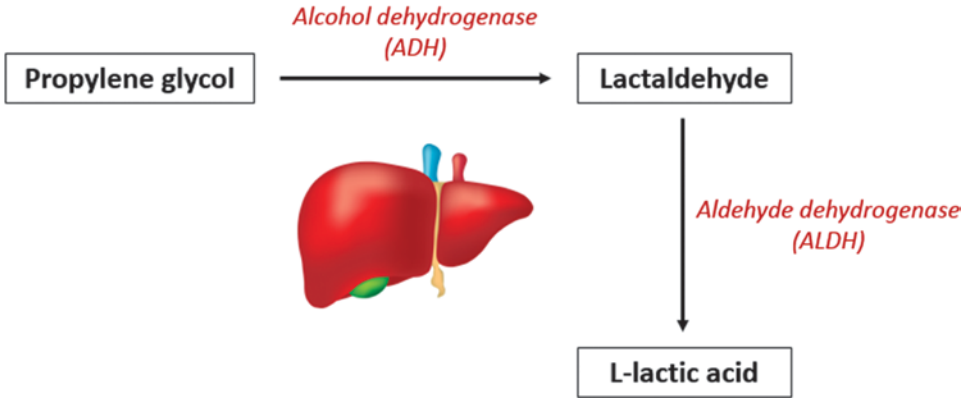


Fig. 6.12 Conversion of propylene glycol to lactic acid in the liver

drug formulations should also be avoided due to their excipients (diluents). For example, injectable itraconazole contains a solubilizing excipient that accumulates in patients with renal insufficiency and is contraindicated in children with a GFR <30 mL/min due to the increased potential for toxicity.

6.10 Summary

In the course of treating critical illness in children, the pediatric intensivist utilizes a broad variety of drugs and therapies. A strong understanding of the science of pharmacology including pharmacokinetic, pharmacodynamic, and pharmaceutical concepts is essential to the care of critically ill patients. Age, organ dysfunction, disease state, co-administered drugs, and therapeutic interventions can all affect drug disposition, effectiveness, and toxicity with potentially significant impacts on patient morbidity and mortality. Whenever uncertainty exists about using a new or infrequently used medication, consultation with a clinical pharmacist or reference resources will help to determine the optimal dosing strategy and to understand how altered organ function and drug interactions may affect the pharmacokinetic and pharmacodynamics properties of the agent.

Review Questions

1. Which of the following is true regarding volume of distribution (V_d)?
   A. V_d is used primarily to determine the frequency of drug dosing.
   B. V_d is typically small for drugs that are highly protein bound.
   C. For most neonates, V_d is smaller due to lower total body water content.
   D. A patient with significant fluid overload would be expected to exhibit a smaller V_d for a specific drug compared to a patient with normal fluid status.
   E. Drugs with a small V_d tend to be widely distributed in peripheral tissues.

2. Which statement best describes the differences between first-order and zero-order elimination?
   A. Zero-order elimination is characterized by a fixed amount of drug removed per unit time; first-order elimination is characterized by a fixed percentage of a drug removed per unit time.
   B. First-order elimination includes the linear Michaelis-Menten or "saturable elimination" model.
   C. Zero-order elimination is common in the initial phases of drug elimination, whereas first-order kinetic often follows after a steady state has been achieved.

D. Zero-order elimination is often seen in the setting of subtherapeutic dosing.
E. Zero-order elimination only occurs with highly protein-bound drugs.

3. Which of the following is a phase I hepatic metabolism reaction?
A. Glucuronidation
B. Methylation
C. Hydrolysis
D. Sulfation
E. Conjugation to glycine

4. Which one of the following statements regarding the effects of therapeutic hypothermia on drug disposition is true?
A. Hypothermia generally increases the effectiveness of medications.
B. The major effect of hypothermia on drug metabolism is caused by an increased affinity of drug molecules for the cytochrome p450 enzymes.
C. Hypothermia increases drug distribution into the central nervous system.
D. Hypothermia decreases hepatic metabolism by reducing the function of the cytochrome p450 enzymes.
E. The effects of hypothermia have been demonstrated mainly in the absorption and distribution phases of drug pharmacokinetics.

5. Which statement does *not* reflect the known effects of an extracorporeal membrane oxygenation (ECMO) circuit on drug disposition?
A. The ECMO circuit may decrease the plasma concentration of a drug by increasing its volume of distribution.
B. Free drug concentration may be decreased by binding to the polyvinyl chloride tubing of the ECMO circuit.
C. Free drug concentration may be decreased by adsorption to the ECMO oxygenator.
D. Patients who require ECMO often have coexisting organ failure which contributes to alterations in drug kinetics.
E. The ECMO circuit enhances hepatic drug metabolism by inducing cytochrome p450 enzymes.

Answers

1. B

Volume of distribution (V_d) is a theoretical value representing the plasma volume required to contain an entire administered dose of a drug based on its concentration in the plasma. Drugs that distribute extensively outside the intravascular space into peripheral tissues have a larger V_d. A high degree of binding to plasma proteins tends to keep drugs in the intravascular space; therefore, drugs with a high degree of protein binding have a smaller V_d. Volume of distribution is not particularly helpful in determining the frequency of drug administration; however, knowledge of V_d can assist with determining loading and reloading doses of certain medications. As neonates have a higher percentage of body water compared with older children and adults, V_d for many medications is higher in this population (e.g., gentamicin). A patient with severe edema or fluid overload would be expected to have a higher V_d for most hydrophilic medications as increased third-space and interstitial fluid provides a larger volume into which the drug may distribute.

2. A

A drug that is removed from the body as a fixed percentage over time is described as having first-order elimination. (see Fig. 6.10 in the text).

First-order kinetics implies that the elimination mechanisms are not yet saturated, so a higher concentration of drug should lead to a higher quantity eliminated in that time interval (the percent eliminated is a fixed quantity). Under first-order kinetics, dose adjustments are expected to produce proportional changes in serum concentration. Most drugs used at therapeutic concentrations are eliminated via first-order kinetics. Zero-order elimination occurs when a fixed amount of drug (rather than percentage) is removed per unit time, and the linear plot of drug concentration versus time demonstrates linear decay. Zero-order kinetics implies a saturation of the elimination mechanisms. Many drugs display first-order kinetics initially, but at higher concentrations when elimination pathways become saturated, removal of the drug becomes zero order; therefore, this type of elimination is often seen in the setting of supra-therapeutic dosing or an overdose. The Michaelis-Menten model describes enzyme kinetics that approach a maximum rate (V_{max}). At lower doses, drug elimination follows first-order kinetics but once the elimination mechanisms reach V_{max}, elimination becomes zero-order.

3. C

Hepatic drug metabolism is generally classified into either phase I or phase II reactions. Phase I reactions are *modification reactions* that include hydrolysis, reduction, oxidation, and cyclization/decyclization. These reactions serve to introduce polar groups to exogenous drug molecules, which limits transport through cellular membranes and enhances renal elimination. Phase I reactions may also convert a parent drug to an active metabolite. Phase II reactions are *conjugation reactions* whereby a charged or polar group (e.g., glutathione, sulfate, glycine, methyl, glucuronic acid) is added to the drug molecule. This serves to increase the metabolite's molecular weight and charge, making it less reactive and more likely to be excreted. Of the choices listed, only hydrolysis is considered to be a phase I reaction as it involves modification of the drug by reaction with a water molecule and not conjugation to a new functional group.

4. D

During therapeutic hypothermia, the function of the hepatic cytochrome p450 system is reduced, thereby decreasing the metabolism and clearance of drugs that interact with this enzyme family. Reductions in clearance during hypothermia are observed for many hepatically metabolized drugs including fentanyl, morphine, barbiturates, propofol, vecuronium, propranolol, and phenytoin, among others. Proposed mechanisms for hypothermia-induced reduction in activity of the p450 enzymes include a reduced rate of redox reactions, decreased substrate affinity, and changes in enzyme binding pocket conformation. In addition to impairing hepatic metabolism, hypothermia may also reduce the effectiveness of certain drugs. Morphine is hepatically metabolized by both phase I (p450 enzymes) and phase II (glucuronidation) reactions; thus, its clearance may be impaired by hypothermia. However, animal studies show that morphine has reduced affinity for the μ-opioid receptor as body temperature decreases, thereby reducing its potency. Hypothermia has not been described to increase drug transport into the central nervous system; rather, some animal studies have demonstrated hypothermia may provide a protective effect in preventing disruption in the blood-brain barrier.

5. E

The use of ECMO may be a lifesaving therapy for many patients with critical illness, but the circuit has well-described effects on drug disposition. The addition of an ECMO circuit to a patient's native circulation creates a larger

volume of distribution for many drugs that may require adjustments in loading and reloading doses. The circuit tubing and oxygenator may sequester drugs via adsorption of drug molecules, thus decreasing the plasma concentration of free drug. It is important to recognize that many patients who require ECMO also have coexisting failure of one or more organ systems, making the effects of the ECMO circuit on drug pharmacokinetics difficult to distinguish from the effects of critical illness. Finally, while induction of cytochrome p450 enzymes is known to enhance metabolism of many drugs, there is no known effect of ECMO on induction or inhibition of liver enzymes.

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Respiratory

Contents

Pulmonary Structure and Function

Jonathan Spahr

Contents

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Learning Objectives

- Describe key points in human lung embryology
- Understand the transport of gas through the conducting airways to and from the alveoli
- Understand the structure of the airways and their properties
- Describe the two sources of blood supply to the lungs
- Understand and contrast dynamic and static compliance
- Understand compliance of lung, chest wall, and total respiratory system
- Describe hysteresis and its causes
- Understand the function of and unique properties of lung surfactant
- Understand the determinants of airways resistance and the differences between laminar and turbulent flow
- Understand and use the alveolar gas equation to assess oxygenation defects

This chapter will review how the normal lung should function while highlighting disease that disrupts normal function. A brief review of lung development will be presented, followed by lung anatomy and, finally, lung physiology. It is important to understand lung development in the context of lung anatomy because there can be disruptions in the development of the respiratory system that can contribute to disease. Furthermore, the arrangement of the respiratory system has important implications for how well the lungs function in the vital process of respiration, namely, oxygenation and ventilation.

7.1 Developmental Biology/Anatomy

An understanding of how the respiratory system develops supports a knowledge of anatomy of the lungs. It also allows for an understanding of how lung anomalies may arise if insults to the normal lung development occur during certain phases of gestation.

Lung development has its beginnings very early in fetal development. In week 4 of embryonic development, the lungs are formed by the projection of the lung bud (laryngotracheal groove) from the ventral foregut. By weeks 5 and 6, the left and right lungs push into what will be the pleural cavity and descend into the thorax. In gestational week 7, descent of lung and heart structures is curtailed by enlargement of the liver, and by week 17, all the airways have developed within the space that will be the thoracic cavity. The airways then continue to differentiate into respiratory bronchioles, and acinus formation occurs. The acinus is the basic unit of the lung and will be discussed in more detail in a subsequent section. From gestational age 26 weeks to adolescence, the lung develops into the organ with the primary responsibility of respiration. This stage of lung development is crucial for creating functioning alveolar units and increasing surface area needed for gas exchange. These stages of lung development are highlighted in ◘ Table 7.1.

The structure of the airways in the lung have developed by gestational week 17.

Gestational age 26 to adolescence is when alveolarization of the lung occurs.

In concert with lung parenchymal development, diaphragm, vascular, and thoracic cavity development occurs. This elegant coordination of lung and respiratory system development, when normally conducted, leads to a normally functioning respiratory system that allows for gas exchange and, most importantly, oxygen delivery to organs and working tissue. When lung and respiratory system development is disrupted, congenital anomalies and/or a deficiency of gas-exchanging units leads to disruption of oxygenation and ventilation. Therefore, understanding the embryologic development of the lung is important to identify why certain disease states occur.

Table 7.1 Stages of lung development

Gestational age	Developmental period	Developmental milestones
3–6 weeks	Embryonic	Lung bud forms and differentiates to segmental bronchi
7–16 weeks	Pseudoglandular	Subsegmental bronchi further differentiate to terminal bronchioles
17–25 weeks	Canalicular	Respiratory bronchioles differentiate and form acini
26–35 weeks	Saccular	Alveolarization and expansion of gas-exchanging units, surfactant production
36 weeks–postnatal maturation	Alveolar	Further alveolarization, maturation of alveolar/capillary interface, lung growth

Embryonic development of the respiratory system reaches a critically important phase encompassing the canalicular and saccular periods (listed in Table 7.1). It is during this phase that development, maturation, and thinning of alveolar structures allow for close approximation with pulmonary capillaries that will take up oxygen and deliver it to the rest of the body. It is also during this critical phase that surfactant production occurs in the type II epithelial cells of the lung. Surfactant is extremely important for promoting normal lung mechanics. Disruption of lung development by preterm birth in the canalicular and saccular periods leads to respiratory distress syndrome (RDS), pulmonary hypoplasia, and subsequent bronchopulmonary dysplasia (BPD) characterized by disrupted lung mechanics and gas exchange. This pathology is characterized by an inability to maintain adequate functional residual capacity (FRC). The importance of maintaining normal FRC will become clear in the subsequent sections of this chapter.

Disruption of gestation (preterm birth) in the canalicular and saccular periods lead to RDS. This is because pulmonary hypoplasia and surfactant deficiency limit the lungs' ability to function properly.

The lung continues to grow after birth both by further alveolarization (addition of and maturation of alveoli) as well as by somatic growth. It is because of this continued growth that neonates and infants with respiratory distress syndrome can recover a significant amount of lung function that similarly injured adults with acute respiratory distress syndrome (ARDS) are less likely to recover. This is one distinction between pediatric and adult lung anatomy and physiology that is dependent upon the development of the lung. Another distinction rooted in the development of the lung has to do with chest wall compliance. The neonate's and infant's chest wall is much more compliant than that of an adult which is supported by fully ossified ribs. This difference is evident both in healthy states and in lung disease as the compliant chest wall is less able to counteract lung elastic recoil. It is most pronounced in lung disease (acute and chronic) where thoracic excursion is limited leading to retractions with paradoxical thorax and abdominal movement. These forces acting upon and between lung and chest wall are important to understand in relation to alveolar ventilation and, ultimately, gas exchange which is the lung's primary task. The next sections of this chapter will focus on normal anatomy and physiology of the respiratory system (lung and thoracic cage) with important examples of aberrant lung pathology to highlight physiologic principles.

A neonate's compliant chest wall makes it difficult for adequate lung excursion to occur. Especially in the case of lung disease that results in non-compliant lung tissue.

7.2 Anatomy of the Lung

The respiratory system consists of the airspace (airways and alveoli) as well as lung parenchyma (interstitium and pulmonary vasculature). Both are acted upon and protected by the pleura, diaphragm, and chest wall. This anatomic arrangement allows for the important task of ventilation, ventilation/perfusion (V/Q) matching, and ultimately gas exchange. The subsequent sections will address how the respiratory system normally functions to perform this important physiologic task. This section will address the anatomic units involved in that task.

7.2.1 Airways

As the laryngotracheal groove buds anteriorly from the ventral foregut, it first forms the tracheobronchial tree. This tracheobronchial tree as it exists in the fully developed individual consists of the trachea that branches into the right and left main bronchi which subsequently branch 23 times until the airways terminate in respiratory bronchioles and alveoli. Larger airways are supported by cartilage to provide a scaffold that maintains airway patency. Disorders in cartilage growth and development such as tracheo- and bronchomalacia lead to airway obstruction, defects in V/Q matching, and defective mucus clearance. Airways distal to the trachea and main bronchi that reach further into the lung parenchyma are supported or tethered by acinar units (lung parenchyma with elastin fibers) and have airway smooth muscle that can contract and decrease the radii of conducting airways. Therefore, diseases which affect how acini are expanded (atelectasis) and smooth muscle contraction (asthma) can influence airway patency. The total cross-sectional area of the conducting airways increases as airflow moves distally allowing for, in a healthy state, unencumbered flow of oxygenated air to the alveoli. This seems somewhat counterintuitive because airways get smaller as air moves more distally. However, the cumulative number of airways leads to a significant increase in total cross-sectional area, and the total amount of conductive airspace is greater at the level of bronchioles in comparison to the trachea and bronchi.

As airways branch distally into the lung, the cumulative cross-sectional area for airflow increases even though airways are much smaller than trachea and bronchi. This cumulative increase in cross-sectional area is helpful in the healthy state as it allows for unencumbered airflow to alveoli. In obstructive airways disease, such as asthma, the cumulative narrowing of these small airways can have a significant impact on ventilation.

As airways branch and narrow, going from bronchi to bronchioles to respiratory bronchioles, they form primary units of the lung defined as the pulmonary lobule which contains acinar units. A terminal bronchiole and acinus together form a lobule. An acinus is a respiratory bronchiole with the alveoli it ventilates. These terms are important to comprehend as lung diseases have patterns that affect lobules and acini. Understanding the distinct anatomic units of the lung helps in interpreting radiographs and pathology specimens. The acinus as a distinct anatomic unit of the lung is important to understand as it has implications on gas exchange and lung compliance.

7.2.2 The Pulmonary Lobule and Acinus

The acinus is the working unit of the lung that completes the main task of the respiratory system; oxygen uptake and carbon dioxide removal.

Airways eventually branch to terminal bronchioles that feed a pulmonary lobule. The lobule contains the terminal bronchiole, respiratory bronchiole, and alveoli. The acinus is the unit of the lung that is supplied by a terminal bronchiole, and so it is comprised of the respiratory bronchiole and alveoli. It can be thought of as the working unit of gas exchange. This is where alveoli exist in close proximity to blood vessels that collect oxygen and dispense carbon dioxide. Every part of the respiratory system functions to ensure adequate

ventilation of the acinar structures for proper gas exchange. This is much like the mitochondria of working cells being supported by the cardiorespiratory system or how the nephron is the working unit of the kidney. Disruption of acinar structure or function can have great effects on the primary function of the lung, gas exchange, as well as lung expansion.

Within the acinus are not only alveoli but a rich network of pulmonary vasculature in the form of pulmonary capillary beds that envelope gas-exchanging alveoli. The arrangement of inflated alveoli to pulmonary capillaries is crucial to the main work of the lung and oftentimes only appreciated when this arrangement is disrupted by disease. Congenital conditions such as alveolar-capillary dysplasia represent a failure of the acinar structure to develop alveoli and capillaries in close proximity and thus result in gas exchange failure. Premature birth leads to a disruption in acinar development (airspace and vascular development) as well as surfactant deficiency which results in less surface area for gas exchange. Acute injury from infection or edema can lead to acinar dysfunction by making it more difficult to diffuse oxygen across diseased alveolar-vascular membranes or by destroying acinar units altogether. Chronic, diffuse disease that affects acinar units can also lead to less surface area for gas exchange.

7.2.3 Pulmonary Vasculature

The lung has 2 sources of blood supply; pulmonary arterial vasculature and systemic arterial vasculature.

The pulmonary vasculature develops along with branching airways, and this concerted development is crucial for ventilation and perfusion matching, necessary for adequate gas exchange. The lung has two sources of blood supply. The main blood supply to the lung comes from the right heart and pulmonary arteries. These vessels carry deoxygenated blood that has supplied working organs and mitochondria with oxygen. They branch along with branching airways and eventually form capillaries that envelop the alveoli (acini) allowing for gas exchange. Capillaries then feed pulmonary veins that return oxygenated blood to the left side of the heart.

The pulmonary vasculature (arterial and venous) is under low-pressure conditions in healthy states. Hypoxemia, disrupted lung development, and pulmonary vascular disease can all affect how blood supplies the lung and acinar units. In the case of hypoxemia, the pulmonary arteries limit blood flow to lung units (lobules and acini) that are not ventilated adequately. This is advantageous in acute disease as it can preserve ventilation and perfusion matching. It can be disadvantageous in chronic disease as this vasoconstriction can eventually lead to chronic vasoconstriction, arteriole wall thickening, and pulmonary hypertension (PH). In cases such as BPD where pulmonary vascular development is disrupted, pulmonary arterioles and capillaries can be in short supply for working acini to transfer oxygen to pulmonary blood. Finally, primary pulmonary hypertension (in contrast to secondary PH that develops from lung disease and chronic hypoxemia) can limit blood supply to working acinar structures, disrupting ventilation and perfusion.

The second source of blood to the lungs is from the left side of the heart. This blood source, like blood supply to other vital organs and working muscles, is oxygenated blood that supplies working tissue of the lungs. This blood supply consists mainly of bronchial arteries that feed the airways of the lungs. Bronchial arteries arise from the aorta and drain to the azygos veins. In chronic, suppurative lung disease like bronchiectasis, or disease states that cause pulmonary hemorrhage, understanding that the lungs have both pulmonary arterial blood flow that is under relatively low pressure and systemic, or bronchial,

arterial blood flow which is under relatively high pressure can be clinically relevant. In cases of pulmonary hemorrhage from pulmonary arterioles, the bleeding may not be particularly brisk. In fact, some individuals with pulmonary bleeding syndromes may not have hemoptysis as a presenting sign. In contrast, bleeding from bronchial artery supply is very significant and can cause massive hemoptysis. Understanding the severity of bleeding and the anatomy of pulmonary blood flow will allow the astute clinician to better localize the source of pulmonary bleeding.

7.2.4 Pleura/Chest Wall/Diaphragm

The pleura, chest wall and diaphragm are crucial for ventilation as well as protection of the lungs.

The lung and its components (airways, lobules/acini, blood vessels) are supported and acted upon by the thoracic cavity. The thoracic cavity consists of the pleura, chest wall, and diaphragm. These components are crucial for housing lung structures, protecting lung structures, and, most importantly, moving (ventilating) lung structures to bring oxygen containing air into the lung and to move the by-product of metabolism (carbon dioxide) out of the lung.

The next section of this chapter will highlight just how important the thoracic cavity is to the process of ventilating the lung. However, it is important to highlight again the difference between an infant thoracic cavity and that of an older child/adult thoracic cavity. The main difference is in the supporting cartilaginous and ossified ribs. In infants, the chest wall is supported by a significant amount of compliant/cartilaginous rib structure. Therefore, a more compliant chest wall can make it difficult to counteract lung elastic recoil especially in disease states. In acute disease, infants can display more signs of respiratory distress such as suprasternal and subcostal retractions than adults. In chronic disease, infants can have significant problems with failure to thrive because the metabolic demand of breathing can be amplified in an infant with difficulties breathing with a compliant chest wall. Merely maintaining adequate FRC can be a significant problem for infants with lung disease and noncompliant lungs. This should become clearer in the next section of lung physiology.

7.3 Lung Physiology

Up until this point, the anatomy of the respiratory system has been discussed. Again, understanding how the respiratory system is normally developed and arranged is important to understanding how the respiratory system works: respiratory physiology. An emphasis on normal physiology will be presented with examples of disease that disrupt normal function.

FRC is the “steady state” of the lung in which elastic recoil of the lung is equal and opposite to elastic recoil of the thoracic cavity. Disruption of FRC by disease leads to increased work of breathing and disruption of adequate ventilation.

The respiratory system without movement at end exhalation is in a balance between the chest wall and diaphragm pulling outward against the lung recoiling inward. This point at which the two forces are equally opposing is functional residual capacity (FRC). The respiratory system is only part of the time at FRC and the rest of the time it is in motion. When the lung is in motion and ventilating, the chest wall and diaphragm need to overcome forces in order to move air into and out of the lung. Understanding these forces helps clarify normal pulmonary physiology and how normal lung mechanics can be disrupted. These forces that impede ventilation/respiratory movement can be broadly broken down into two main categories: the elastic forces that impede chest movement (lung compliance) and the resistive forces that impede airflow or airways resistance.

7.3.1 Lung Compliance/Elastance

Lung compliance is a measure of how much of a change in pressure is needed to make a change in volume of air inspired/expired.

Lung compliance is a measure of how deformable the lungs are: a measure of the lungs' ability to move. It can be calculated as static or dynamic and is obtained by dividing the change in volume by the pressure needed to make that change ($C = \Delta V / \Delta P$). The measure of compliance of the whole lung is transmural pressure. This is the difference in pressure that is measured from the alveolar space to the pleural space. Transmural pressure equals alveolar pressure minus pleural pressure ($P_{tm} = P_{alv} - P_{pl}$).

Lung elastance is simply the reciprocal of compliance, and it is dependent upon elastin fibers in the parenchyma but, in the healthy lung, more dependent upon surface tension of the alveolus. Since there are over 300 million alveoli in the lung, the surface tension of alveoli has a profound impact on the overall compliance, or elastance, of the lung. The additive result of millions of alveoli with their individual surface tension characteristics can be analyzed as a whole. It is important to realize, however, that lung disease is not uniform, and variably affected areas of the lung will have differing surface tensions and, consequently, varying lung compliance. This is exemplified in ARDS. For the purposes of better understanding lung compliance, however, the cumulative effects of surface tension on lung compliance are important.

The law of Laplace relates the pressure over a liquid surface within a sphere or cylindrical vessel, to the area of that surface, and the surface tension of the liquid. It is represented in the following equation:

$$P = 2T / R$$

where P is pressure, T is surface tension, and R is the radius of a cylinder or bubble (or in the case of the lung, alveolus). In the case of the alveolus, the surface tension is very important in determining pressure required to maintain inflation of the alveolus. In the case of the lung, the pressure required for distention of the alveolus or many alveoli is very important in determining compliance of the lung. Lung compliance is dependent upon pressure gradients across the lung and the relationship of change in pressure to change in volume. Therefore, surface tension as a major component of alveolar pressure is critical in determining how well the lung functions. The components of alveolar surface lining liquid determine surface tension and the ease at which the lung inflates. The vital surface tension lowering component of the alveolar lining is surfactant.

One of surfactant's critical characteristics is its ability to vary its surface tension properties across varying radii/alveolar volumes. According to the Laplace equation, as surface tension increases, so should pressure in the alveolus. Pressure and surface tension are proportional. However, pressure and radius (or, in the case of the lung, pressure and alveolar volume) are inversely proportional. As the radius of the alveolus increases, the pressure inside should decrease, and as the radius of the alveolus decreases, the pressure inside should increase. If surface tension were to remain constant, then alveoli of smaller volume would have required higher distending pressures, and gas would preferentially move from smaller to larger alveoli. Smaller alveoli would be more difficult to remain open, and larger alveoli would tend to increase in size. This would be quite disadvantageous in the lung as poorly ventilated or atelectatic lung units would remain atelectatic, and larger or emphysematous lung units would become more and more emphysematous.

If surface tension in the lung were constant, alveolar volume of large alveoli would increase leading to emphysema, and alveolar volume of small alveoli would decrease leading to atelectasis. Surfactant is important to maintaining normal lung compliance because it can vary surface tension and, in turn, balance compliance across the lung.

Fortunately, surfactant has the special ability to decrease surface tension at low lung volumes and increase surface tension at high lung volumes. Therefore, surface tension is a variable, not a constant. This is shown in the equation below where pressure can remain constant in the face of varying radii (alveolar volumes):

$$2 \downarrow T / \downarrow R = P_{alv} = 2 \uparrow T / \uparrow R$$

Maintaining a constant alveolar pressure (P_{alv}) is highly important to maintaining a constant transmural pressure which determines how well the lung can perform its mechanical work (ventilate).

7.3.2 What Is Surfactant?

Surfactant is the substance produced in alveolar type II cells that allows surface tension to increase at high lung volumes and decrease at low lung volumes. How surfactant is composed allows this to happen. Surfactant is 90% lipid, and 70–80% of the lipid is dipalmitoyl phosphatidyl choline (DPPC). It is the nature of surfactant DPPC which gives its varying surface tension properties. Ten percent of the composition of surfactant is protein of which surfactant proteins comprise about 2%. These surfactant proteins B and C are very important and responsible for controlling the release and stabilization of surfactant in the alveoli. Infants born with the absence of surfactant protein B (SPB) and ATP-binding cassette member A3 (ABCA3) will have severe respiratory distress and failure. This will also occur to a lesser degree with other surfactant protein deficiencies. Surfactant proteins A and D belong to a family of immune proteins called collectins and are involved in pathogen recognition and immune cell regulation.

Other clinical situations in which surfactant function can be disrupted are neonatal respiratory distress syndrome, ARDS, and congestive heart failure (CHF). All are clinical entities that perturb the natural function of surfactant and lead to poor lung compliance, leading to inadequate ventilation.

Deficient, defective and displaced surfactant in the diseased lung leads to a state of non-compliant lung.

In neonatal RDS, a baby is born at a premature age prior to adequate lung development and maturation of alveolar type II cells. Hence, the premature neonate is born with a surfactant deficiency. As the baby transitions from a liquid environment in the uterus to an air environment, amniotic fluid in lungs needs to be expelled to replace fluid-filled alveoli with air-filled alveoli. As some alveoli do not completely expand, heterogeneity occurs among lung units, and gas will preferentially redistribute from smaller alveolar units to larger units in the absence of surfactant (Laplace's law). Volume loss in some lung units occurs in conjunction with overinflation in others. Atelectasis can occur in conjunction with emphysema or even air leak/pneumothorax.

The same may occur in ARDS but by a different mechanism. While in neonatal respiratory distress syndrome the problem is a lack of surfactant production, ARDS is a problem of a loss of functional surfactant. This loss of functional surfactant in conjunction with damage from inflammation leads to poor lung compliance and alveolar volume loss in some lung units with overinflation in other.

In CHF the problem is increased lung water. Surface tension of simple liquids (such as edema) is much higher and not variable like surfactant. With transudation of fluid into alveoli in CHF, the action of surfactant is diluted, and surface tension (T) increases which also increases the pressure (P) needed to distend alveoli. Increased P causes a decrease in lung compliance.

7.3.3 Transmural Pressure and Volume

Lung compliance, the ability to change volume based on a distending pressure, can be understood with regard to surface tension and surfactant. In the context of lung disease, it is important to understand how compliance affects the lung during ventilation, the lung that is changing volume from FRC to inflating volume and back. Fortunately, compliance is relatively constant in the healthy lung. This is important because it allows for varying transmural pressures to accommodate for varying lung volumes in the different zones of the lung. Looking at the equation, $C = \Delta V/\Delta P$, if C is relatively constant, this allows for ΔV to change relatively constant with ΔP.

At the apices, pleural pressure is more negative causing a greater transmural pressure gradient. At the bases, where pleural pressure is less negative, there is a smaller pressure gradient. Along with these differences in pressure gradients, there is a coincident change in volume, and so the compliance throughout the lung remains relatively constant in the healthy lungs among lung zones and within normal tidal breathing volumes. In $C = \Delta V/\Delta P$, if rearranged to $\Delta V = (C)\Delta P$, then ΔV is directly related to ΔP. This is very important in maintaining normal lung function and can be significantly disrupted in disease that affects lung compliance. If compliance (C) decreases, then the distending pressure (ΔP) needed to maintain a normal volume (ΔV) needs to increase.

ΔV is proportional to ΔP as long as lung compliance is preserved. Disease states that disrupt normal lung compliance disrupt the relationship between ΔV and ΔP, in that, higher pressures in a non-compliant lung are needed to maintain adequate ventilating volume.

In diseases like ARDS where there is heterogeneous damage that occurs, it is easy to see why a constant compliance throughout the lung is so important. If ARDS is a heterogeneous disease with differing compliances throughout the lung parenchyma, then differing pressure gradients will be needed to ventilate different areas. More compliant areas will require less pressure and run the risk of overinflation (air leak/pneumothorax), while less compliant areas will require higher pressure gradients (ΔP) to ventilate (ΔV) and are at risk for collapse if those areas are not adequately ventilated (atelectasis).

7.3.4 Hysteresis

Lung compliance has two components: static compliance and dynamic compliance. If the lung is inflated to a level and held, there is an initial peak pressure required to fully inflate and then a decline to a plateau where this new level of pressure maintains volume. Thus, there is a time dependence on the elastic behavior (compliance) of the lung. In other words, compliance changes during phases of breathing or lung inflation. Additionally, static compliance is measured at a point where flow has ceased and thus contains no component of airways resistance. Dynamic compliance is measured during inflation where airways resistance may contribute to inflation pressure requirement. The measured compliance during inspiratory/inflation and exhalation/deflation is dynamic, while the compliance at the inspiratory plateau and FRC is static compliance.

Static compliance at the same volume varies from inspiration to expiration. There is a difference in the transmural pressure gradient at the same lung volume. This is hysteresis. Interestingly, as tidal volume increases, these points become more distinct. What this means is that during inhalation/inflation, there is a greater required amount of pressure for a given volume than the pressure needed during exhalation (Fig. 7.1).

Hysteresis is the change in compliance related to the phase of breathing and lung volume.

Hysteresis occurs for a number of reasons. First, there are changes in surfactant activity. At high lung volumes, surface tension is higher due to the variation afforded by surfactant. With inspiration, surface tension also tends to be

Surfactant properties contribute to hysteresis because surfactant can vary alveolar surface tension depending on alveolar volume.

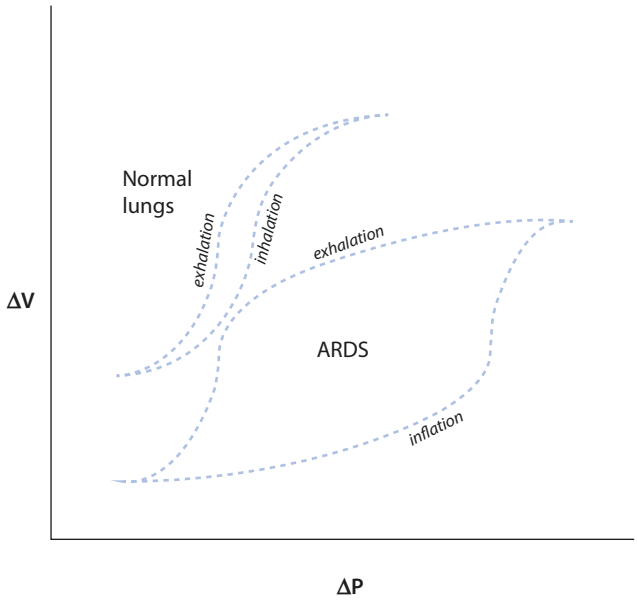


Fig. 7.1 Compliance curves for ARDS: Static compliance curves from a patient with ARDS in comparison to someone with normal lungs. Compliance, especially during inhalation/inflation, is reduced in ARDS as shown by the slope of the line and markedly so at low and high lung volumes

higher than in exhalation. A second component of hysteresis is stress relaxation. The initial pressure to move the lung at rest needs to be greater than the pressure needed to continue to move the lung in motion, much like the coefficient of static friction is often greater than the coefficient of kinetic or dynamic friction. A third component relates to time constants and redistribution of gas that occurs. This is based on airways resistance and lung compliance. Pulmonary time constants describe the amount of time taken to fill or empty a lung unit, and mathematically the time constant is the product of the airways resistance times the lung unit compliance. The units for airways resistance are mmHg/mL/second (or mmHg x second/mL), and the units for compliance are mL/mmHg; thus their product is seconds, the time for lung unit filling or emptying. A lung unit will fill to 63% of its capacity in one time constant and to 96% of its capacity in three time constants. Fig. 7.2 shows how different lung units fill and eventually redistribute air (volume) within the lung. Finally, and this situation likely only occurs in disease states and in the first few breaths of a neonate, recruitment of non-distended alveoli can make for a situation in which initial distending pressures need to be higher to "pop" open collapsed alveoli.

7.3.5 Factors Affecting Compliance

In the diseased lung, compliance can be affected by many factors. Both static and dynamic compliance can be affected.

First, lung volume affects compliance. In an emphysematous lung, compliance is increased, whereas in a lung with restrictive disease (e.g., pulmonary fibrosis), compliance is decreased. Acute respiratory distress syndrome is an example in which static compliance of the lung is greatly decreased in some areas and may be normal in others (Fig. 7.2). Adequate ventilation is challenging in ARDS because of the heterogeneity of compliance in the diseased lung.

Venous congestion within the lung decreases compliance in that more fluid in the lungs makes the lung denser and more difficult to expand. Higher pressures (ΔP) are needed to achieve a change in volume (ΔV). Bronchoconstriction affects dynamic compliance in that an initial high pressure is needed to over-

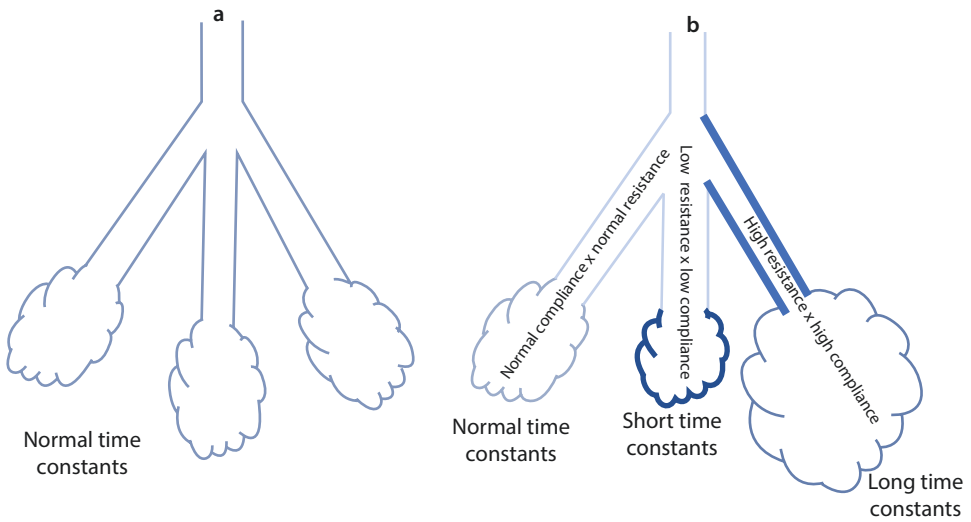


Fig. 7.2 Resistance/compliance characteristics of lung units: When considering airways resistance and lung compliance, the two factors together determine the filling time of the alveolar units (RC time constants). In the normal lung **a** with normal airways resistance and lung compliance, ideally all alveolar units would fill uniformly. With diseased lung **b**, some units may be normal, some may have increased resistance with increased compliance and fill slowly, while some may have decreased resistance with decreased compliance and fill quickly. This heterogeneity of lung units can make alveolar ventilation difficult and is seen in disease states such as ARDS and asthma

come resistance in airways that are constricted. If purely bronchoconstriction, then once the initial dynamic compliance defect is overcome (airways resistance), then static compliance should be normal. This can be seen in asthma. However, as is the case most of the time, there can be atelectasis or loss of lung volume in addition to bronchoconstriction, which can decrease static compliance. Likewise, air leak/pneumothorax can also lead to a loss of lung volume and decrease in static compliance. It is important to fully delineate whether dynamic compliance, static compliance, or both are affected to understand how to treat the problem that is causing poor lung compliance.

Understanding whether static compliance, dynamic compliance or both are disrupted can be useful in determining lung pathology and treatment.

7.3.6 Compliance of the Respiratory System

At this point, only compliance of the lung has been discussed. The thoracic cage itself has its own compliance, and the two (lung and thoracic cage) have a codependent relationship. Compliance of the thorax is also defined as the change in volume divided by the change in pressure. In the case of thoracic compliance, the pressure change is the change in the gradient between atmosphere and the intrapleural space: $C_{thorax} = \Delta V/\Delta(P_{pleura} - P_{atm})$. Compliance of the thorax is primarily dependent upon anatomic factors such as obesity or conditions that may restrict chest wall movement, as well as body position, since the diaphragm in the relaxed state will readily transmit pressure from the abdomen. Pressure from the abdomen, the resistance to diaphragm descent, increases when moving from upright to supine.

When compliance of the lung and compliance of the thoracic cage are considered together, compliance of the respiratory system can be determined. The lung pressure gradient, transmural pressure, is the gradient between alveolus and intrathoracic pressure, and thoracic cage pressure gradient is based on the gradient between intrathoracic and atmospheric pressure. Together, this defines the compliance across the whole respiratory system. When mathematically combining the two equations, the entity intrathoracic pressure drops out. This relationship can be represented as a change in volume over a change in pres-

The thoracic cage is compliant much like the lung is. Together, they both make up respiratory system compliance and is measured as the change in pressure from atmosphere to alveolus that is needed to make a change in volume ventilated.

sure, where the pressure gradient is the difference between alveolar and atmospheric pressure or $C_{total} = \Delta V/\Delta(P_{alv} - P_{atm})$. These various components that determine respiratory system compliance, in turn, have an important impact on FRC.

7.3.7 Determinants of FRC

Functional residual capacity is the volume in the lungs at end expiration when the respiratory system is at a steady state at the end of passive exhalation. It is determined by the thoracic cage forces leading to lung inflation that are equal and opposite to the lung tissue forces leading to deflation. This parameter, FRC, is heavily dependent upon elastic forces of both the lung and the thorax. Therefore, alterations in lung or chest wall compliance or, inversely, elastance can determine how well the lungs are expanded or overexpanded.

Alterations of FRC can occur in multiple different circumstances. Body size and gender can affect FRC. Height increases FRC, while obesity decreases it. Women have on average 10% less FRC compared to men. Reduced respiratory muscle tone can lead to decreased FRC with poor lung expansion and eventual atelectasis. Posture can affect FRC especially in the supine position when abdominal viscera exert pressure on the diaphragm and reduce lung expansion. Finally, disease can have significant effects on FRC. Most pronounced is disease that affects lung and thoracic compliance. It is in disease where one can see the consequences of inability to maintain normal FRC. In restrictive lung disease, FRC is diminished due to increased elastic forces causing the lung and alveoli to collapse if higher distending pressures are not generated to inflate the lung. Functional residual capacity can also be diminished if the thoracic cage is unable to generate enough force to change intrathoracic pressure. This is the case in neuromuscular weakness, where lower lung volumes and FRC will result in lung and alveolar collapse. Conversely, if lung tissue is highly compliant, as in the case of emphysema, FRC will be elevated.

Functional residual capacity can also be affected by airways resistance. If airways are obstructed, then the volume of gas expired from the lung is less and less with each tidal volume/breath. Eventually this will lead to a state of air trapping in the lungs which leads to an increase in FRC.

Restrictive lung disease causes a decrease in FRC. Obstructive lung disease causes an increase in FRC. Any alteration in FRC leads to increased work of breathing to maintain adequate ventilation.

Any deviation from normal FRC means that more work is needed for breathing to maintain adequate lung volumes. Understanding the factors that determine lung compliance, airways resistance, and, ultimately, FRC is important. Subsequent chapters will illustrate how the relationship between ΔV and ΔP (compliance) is so very important to understand in disease states when one is trying to maintain adequate volume expansion of the lung while carefully using and monitoring pressure to adequately ventilate.

7.3.8 Airways resistance

Before alveoli can be distended, air must travel through airways. Airways resistance must also be considered when evaluating how well ventilation occurs. To consider resistive forces to gas flow in the airways, it is important to illustrate and draw distinctions between the two forms of airflow, laminar and turbulent flow.

Laminar flow is defined as flow that consists of concentric cylinders that move over each other and form an advancing cone. The advantage of this flow is that fresh gas in the center of the cone may reach peripheral airways.

Therefore, alveolar ventilation may occur even when the volume of gas delivered is less than that of dead space. This can occur because the center of the "cone" of air depicted in Fig. 7.3 can reach distal airspaces. The disadvantage is that gas at the periphery of the advancing cone may not reach distal airways and may even be stationary. Therefore, with laminar flow, there is a loss of the ability to completely purge the airways of gas. In straight, unbranched tubes, where laminar flow can occur, the resistance to flow is largely dependent upon the radius of the tube as the relationship is dependent upon the fourth power of radius as demonstrated in Poiseuille's law:

The advantage of laminar airflow is that fresh gas may reach alveoli even if the volume of gas is less than dead space.

$$Q = \pi Pr^4 / 8\eta l$$

where flow (Q) is proportional to pressure (P) and radius (r) and inversely proportional to viscosity (η) and length (l). Even slightly decreasing radius (as would be the case in obstructive airways disease – asthma and bronchiolitis) leads to a significant decrease in flow. If the properties of the tube are held constant, and viscosity is the only variable, then changing the viscosity of gas may be advantageous in laminar flow. Viscosity must be distinguished from density of gas.

Turbulent flow is airflow that has a square front (Fig. 7.3). Its disadvantage is that no fresh gas enters distal airways until the full volume of gas is equal to at least dead space. The advantage of turbulent flow is that airways can be purged completely of gas. In turbulent flow, airways resistance is not constant and is proportional to flow rate. Therefore, the ΔP it takes to overcome airways resistance in turbulent flow is dependent upon three principles. First, ΔP is proportional to the square of the flow rate (not to the first order as seen in laminar flow). Second, ΔP is proportional to the density of gas (not viscosity). Third, the required ΔP (to move gas) is inversely proportional to the fifth power of the radius of the tube. As with laminar flow, any decrease in airway radius will have a great effect on airways resistance.

The advantage of turbulent airflow is that airways can be completely purged of gas with adequate ventilating volumes.

Knowing the difference in airways resistance properties between laminar and turbulent flow is clinically important. When trying to overcome airways resistance in a turbulent flow environment, manipulating gas density could be helpful. It is generally accepted that turbulent flow is primarily present in large

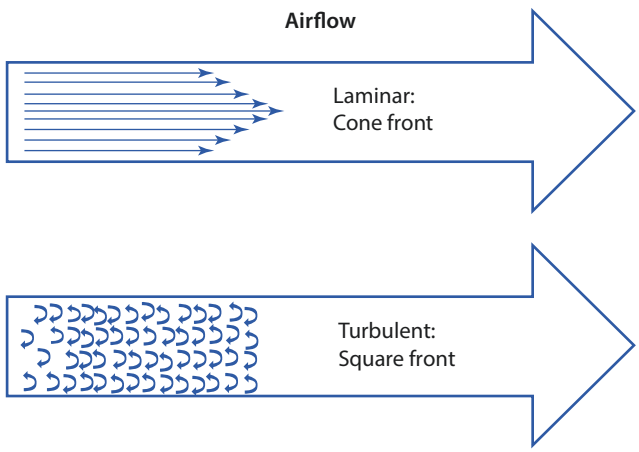


Fig. 7.3 Laminar vs. turbulent flow: Laminar flow (top) establishes a cone of airflow with the central portion of the cone reaching the alveoli even if all of the peripheral portion of the cone does not. In turbulent flow, all the air travels in a square front that necessitates flow all the way to the alveoli for gas exchange to occur. The advantage of laminar flow is that not all the air needs to reach distal alveoli for gas exchange to occur. The advantage of turbulent flow is that gas from the lungs may be completely purged with adequate ventilation

(not small) airways. However, in most clinical scenarios, there is a mixture of laminar and turbulent airflow that is present in all airways. Somewhat counterintuitively, airways resistance has a greater impact on large airways in comparison to the small airways because the total cross-sectional area in the smaller airways is much greater as airways branch distally. Even though the airways are much smaller distally, the vast number of smaller airways contributes to a much larger cross-sectional area for airflow in the smaller airways and bronchioles, greater than the cross-sectional area for airflow in the trachea and bronchi.

With both laminar and turbulent airflow, any decrease in the radii of conducting airways can cause a significant increase in airways resistance.

Other factors that affect airways resistance are lung volume and bronchomotor tone of the airways. Volume is inversely proportional to airways resistance. When there are high lung volumes, airways resistance is less. Higher bronchomotor tone leads to bronchoconstriction and decreased radii of the conducting airways. With decreased radii, the pressure needed to maintain flow through the airways needs to increase or flow will decrease. Clinically, this manifests as increased work of breathing.

7.3.9 Ventilation/Perfusion Matching and Gas Exchange

Knowledge of anatomy and physiology is important to understanding how the lungs perform their most important function: respiration or matching oxygenated air with pulmonary blood supply. This occurs at the level of the pulmonary acinus, and factors of pulmonary compliance and airways resistance greatly determine how oxygenated air gets to the blood supply of the lung at the level of the alveoli.

Gas exchange will be discussed in a separate chapter. However, the concept of ventilation/perfusion matching will be briefly touched upon here. Ventilation is the main purpose of the lung and is dependent upon adequate/normal lung compliance and airways resistance. It is the ability of the lung to deliver oxygenated air to the alveolus where the oxygen can be exchanged across the alveolar/capillary membrane for carbon dioxide, the by-product of metabolism. Understanding how well someone is ventilating and, subsequently, oxygenating can be illustrated in the alveolar gas equation which is

$$P_AO_2 = 0.21\left(P_B - P_{H20}\right) - P_aCO_2 / 0.8$$

Once it is understood how well oxygen is getting to the alveolus, then there can be a better understanding of why someone may not be ventilating adequately. Or it may be that the patient is adequately ventilating, but the acinus is not working properly to exchange gas.

The alveolar gas equation allows for a calculation of alveolar oxygen. Knowing the partial pressure of alveolar oxygen can help determine if hypoxemia is a result of inadequate oxygen delivery (poor ventilation) or inadequate gas exchange at the acinar level (V/Q mismatch, anatomic R→L shunt or diffusion defect).

The alveolar gas equation describes the causes of hypoxemia. Considering the components of the alveolar gas equation will allow for an understanding of how oxygen gets to the alveolar space and is available for diffusion across the membrane into the blood. Oxygen exists in the environment as a fraction of the air that is inspired (0.21). Because it is a partial pressure of oxygen, it is a fraction (0.21) of the pressure of air (P_B) that must also subtract out other molecules in ambient air from the environment and the airways. These other molecules are mostly water (P_{H2O}). When this fraction of oxygen reaches the alveoli, other gas particles are present, and this is primarily carbon dioxide (P_aCO_2). Because the displacement of O_2 by CO_2 in the alveolus cannot be measured directly, it must be calculated from the arterial CO_2 by dividing by the respiratory quotient (R, commonly estimated as 0.8). Once the amount of oxygen that is supplied to the alveoli (P_AO_2) is known, then it can be better

understood how well, or how poorly, the lungs are working in the act of gas exchange.

Consider the five main causes of hypoxemia (Table 7.2): ventilation/perfusion (V/Q) mismatch, anatomic shunt, diffusion defect, hypoventilation, and altitude (or decreased ambient air pressure). In the case of hypoventilation, the alveolar gas equation explains why hypoxemia occurs. It occurs because not enough oxygen is delivered to the alveolus. P_aCO_2 will rise because of inadequate ventilation, and subsequently P_AO_2 will fall. Likewise, in the case of altitude, not enough oxygen is delivered to the alveolus. In this case, a lower P_B decreases, and the amount of ambient oxygen inspired is decreased.

In the cases of V/Q mismatch, anatomic shunt, and diffusion defect, the lungs are able to ventilate and get oxygenated air to the alveolus (or at least some alveoli), but there is a problem at the acinar level with the oxygen. In V/Q mismatch, there is regional hypoventilation and physiologic shunting of blood through areas of the lung that are not well oxygenated. This is the case with atelectasis or pneumonia. One part of the lung is unable to ventilate well, and so hypoxemia may occur. This can be overcome by increasing ventilation and perfusion to healthy areas area of the lung that can compensate. Also, supplemental oxygen may help compensate for hypoxemia in areas of low V:Q ratio but not where V:Q = 0, defined as true or absolute shunt.

In anatomic right to left shunting, the alveoli are adequately ventilated, and P_AO_2 is normal, but blood flow is shunted around the alveoli either at the cardiac level or by pulmonary arteriovenous malformations. In this situation, supplemental oxygen will be ineffective in correcting the hypoxemia.

Finally, in diffusion defect, the alveolar-capillary interface is disrupted so that oxygen does not easily diffuse into the pulmonary blood supply. In this case, oxygen supplementation, to a degree, can help correct hypoxemia.

As illustrated above, when considering hypoxemia due to V/Q mismatch, anatomic shunt, or diffusion defect, supplementing oxygen can be beneficial in narrowing down the cause of hypoxemia. It should be stressed that supplementing oxygen should be carefully considered as a therapy only after hypoventilation as a cause of hypoxemia has been ruled out. Supplementing oxygen will have no benefit in the case of pure hypoventilation as the patient is unable to ventilate to get oxygen to the alveoli in the first place.

One can further narrow down the cause of hypoxemia by supplementing oxygen and assessing for a response. In the case of anatomic shunt, oxygen supplementation will have little to no effect on improving oxygenation.

In the situation where ventilation appears to be adequate, the problem is with inadequate oxygen delivery to the pulmonary capillary blood supply. In this case, an increased alveolar-arterial (A-a) gradient exists:

$$P_AO_2 - P_aO_2 = A - a\ \text{gradient}$$

Normal A-a gradients range from 3 to 8 mmHg for healthy children and adolescents. If oxygen is adequately delivered to the alveolar level (A) but not adequately delivered to pulmonary capillaries and subsequently systemic

Elevated A-a gradient indicates that there is poor oxygen delivery to the vascular bed at the level of the acini/alveoli.

Table 7.2 The five causes of hypoxemia with effects on P_aO_2 and A-a gradient

Five causes of hypoxemia	P_AO_2	A-a gradient
V/Q mismatch	Normal/↓	↑
Anatomic R → L shunt	Normal	↑
Diffusion defect	Normal	↑
Hypoventilation	↓	Normal
Altitude (↓FiO2)	↓	Normal

arteries (a), then an increased gradient exists, and hypoxemia occurs. In the case of inadequate ventilation or altitude, the A-a gradient should be normal because arterial oxygen (P_aO_2) is low because alveolar oxygen tension (P_AO_2) is low. Of course, in practice, there is often a combination of inadequate ventilation and alveolar gas exchange. So the alveolar gas equation and the A-a gradient must always be interpreted with clinical context. Nevertheless, understanding how oxygen is delivered to the alveolus (ventilation) and how it is subsequently delivered to the pulmonary vasculature (oxygenation) will be very important when evaluating and treating patients with respiratory distress and hypoxemia.

Knowing how respiratory compliance and airways resistance affect ventilation is essential for evaluating a child with increased work of breathing and impending respiratory failure. Finally, knowing the difference between inadequate ventilation and alveolar gas exchange (oxygenation) is essential for assisting children with respiratory distress and respiratory failure. Subsequent chapters that discuss respiratory failure, ARDS, and mechanical ventilation will highlight these important physiologic principles.

7.4 Summary

The lung and respiratory system arise early in gestation and give rise to an anatomic structure that allows for normal physiologic function. Disruption of normal development can affect normal anatomic structure and, ultimately, function. Normal respiratory physiology has its roots in normal developmental anatomy. Neonatal respiratory distress syndrome and BPD are prime examples of how disruption of normal developmental anatomy can have a significant impact on normal lung physiology. There are other examples of lung disease that impact normal physiologic function as well. A knowledge of lung physiology is important for the clinician when treating pediatric lung disease. First, it must be appreciated that lung physiology in children differs from adults mainly because lung and chest wall compliance in children is different from adults. Second, understanding how the forces of respiratory system compliance and airways resistance impede ventilation is critical because disease states only augment the factors that impede normal ventilation. Finally, understanding how gas exchange at the acinar level is affected by ventilation (or inadequate ventilation) allows for a better understanding of why patients with lung disease have respiratory insufficiency or failure. With this understanding, the clinician will be equipped to identify and treat the cause of respiratory disease.

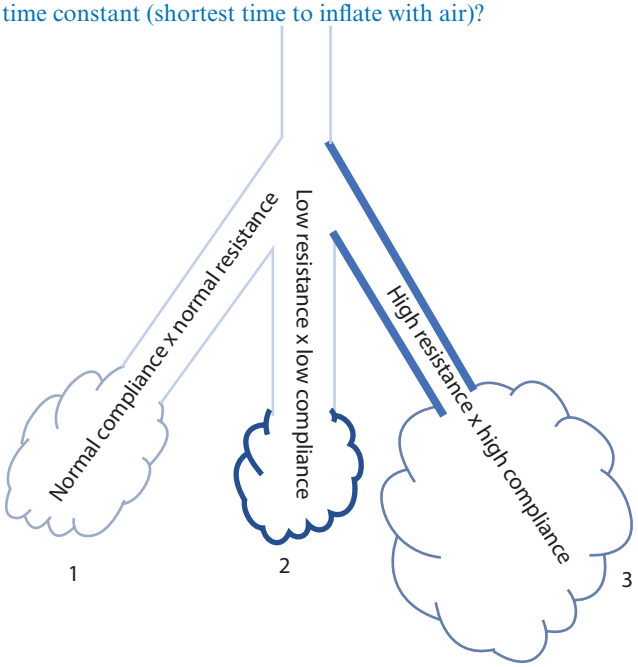
Five Multiple Choice Questions

1. The saccular stage of lung development continues the development of alveoli and is the initiating phase of surfactant production. At what point in gestation does the saccular stage begin?
   A. 4 weeks
   B. 17 weeks
   C. 26 weeks
   D. 36 weeks
   E. 40 weeks

2. What level of the airways presents the least resistance to airflow in healthy lungs?
   A. Nose
   B. Oropharynx

C. Trachea
D. Large airways
E. Small airways

3. Which of the following acini in the diagram below would have the shortest time constant (shortest time to inflate with air)?



A. 1
B. 2
C. 3
D. 1 and 3
E. 2 and 3

4. A 14-year-old with history of BPD is admitted to Floating Children's Hospital in Boston with a right lower lobe pneumonia. He has an oxyhemoglobin saturation of 86% breathing room air. His respiratory rate is 44, and he has nasal flaring. You obtain an arterial blood gas while he is breathing room air, and the values are pH 7.42, P_aCO_2 40, P_aO_2 50. What is his A-a gradient?
A. 18
B. 36
C. 50
D. 100
E. 110

5. In the patient above, you supplement oxygen with 50% face mask via venturi valve. His oxyhemoglobin saturation improves to 96%, and you obtain another arterial blood gas. The values are pH 7.44, P_aCO_2 36, P_aO_2 296. In this scenario, what is the most probable cause of his hypoxemia?
A. Hypoventilation
B. Decreased inspired oxygen tension
C. Anatomic right→left shunt
D. Diffusion defect
E. Ventilation/perfusion mismatch

Answers

1. C – 26 weeks. The saccular stage begins around gestational age 26 weeks. This is when respiratory bronchioles and alveoli develop in the acini and type II pneumocytes begin to produce surfactant. Disruption of gestation in the canalicular period (which precedes saccular) and saccular period leads to RDS. What results is pulmonary hypoplasia because of acinar and vascular immaturity as well as surfactant deficiency. Surfactant is critically important for maintenance of normal lung compliance. At 4 weeks gestation, the ventral groove of the foregut buds to initiate respiratory tree formation. By 17 weeks, the majority of airways have been formed. At 36 weeks begins the alveolar phase when alveoli develop and mature into adolescence.
2. E – small airways. The cross-sectional area of all the small airways is cumulatively larger than either trachea, bronchi, or upper airways. Therefore, the overall resistance to airflow at the level of small airways (generally believed to be the 11th generation and beyond) is lower than that of the nose, oropharynx, trachea, or bronchi.
3. B – 2. A lobule/acinus with poor compliance (low compliance) and low airways resistance will have the shortest filling time (RC time constant). This is because airways resistance is low allowing for faster transit time through the airway, and lung compliance is low causing rapid filling of the airspace. Both airways resistance and lung compliance being low lead to a short time constant. In ARDS, which is a heterogeneous lung disease, there are varying resistances and compliances (RC time constants) throughout the lung. This makes treating ARDS with mechanical ventilation a challenge.
4. C – 50. If breathing room air, the fraction of inspired oxygen is 0.21. Barometric pressure at sea level would be 760 mmHg and partial pressure of H_20 47 mmHg. Using the alveolar gas equation, this child has a P_AO_2 of 100 ($P_AO_2 = 0.21(760–47) – 40/0.8$). If his P_AO_2 is 100 and his P_aO_2 is 50, then his A-a gradient is 50.
5. E – ventilation/perfusion mismatch. V/Q mismatch is the most common cause of hypoxemia in children with lung disease (acute and chronic). In this case, V/Q mismatch is most likely because of a widened A-a gradient that improves oxygenation with supplemental oxygen. Diffusion defect is also a possibility for someone with a widened A-a gradient that improves with oxygen, but in this clinical scenario, with a child who has a lobar pneumonia, ventilation and perfusion mismatch is more likely because of regional disruption of ventilation accompanied by preserved or diminished perfusion.

Suggested Readings

Nunn's Applied respiratory physiology. 8ed: Elsevier.
Kendig's Disorders of the Respiratory Tract in Children. 8th Ed: Saunders.
Pediatric Respiratory Medicine (Taussig and Landau). 2nd Ed: Mosby/Elsevier.
Respiratory Physiology – The Essentials (West) – 10th Ed: Wolters Kluwer.

Fundamentals of Gas Exchange and the Assessment of Oxygenation and Ventilation

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Contents

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Learning Objectives

- Present and explain the alveolar gas equation and describe the changes in the partial pressure of oxygen from the atmosphere to the bloodstream.
- Define dead space (alveolar and anatomic) and describe its quantification and describe the compensatory mechanisms invoked with increased dead space.
- Describe the distribution of ventilation and pulmonary blood flow.
- Describe how ventilation and perfusion are coupled and detail common causes of their uncoupling.
- Describe the alveolar/arterial oxygen gradient and demonstrate its calculation.
- Describe the transport of gases within the body and focus especially on the hemoglobin/oxygen dissociation curve and carbon dioxide transport.
- Describe the differences between oxygen and carbon dioxide transport.
- Describe the mechanics of, uses, and limitations of pulse oximetry, end tidal carbon dioxide monitoring, and transcutaneous oxygen and carbon dioxide measurement.

8

8.1 Introduction

The basic function of the respiratory system is to supply oxygen (O_2) to, and remove carbon dioxide (CO_2) from, the body. The essential steps in this process include the exchange of gas between the atmosphere and the alveoli (ventilation), the diffusion of these gases across the alveolar capillary membrane, the transportation of gases in the blood, and the diffusion of the gases to and from the tissue capillaries.

8.2 The Process of Gas Exchange

8.2.1 Alveolar Ventilation and the Oxygen Cascade

In normal lungs, because carbon dioxide diffuses so readily across the alveolar capillary membrane, the alveolar CO_2 (P_ACO_2) is essentially equal to the arterial carbon dioxide ($PaCO_2$).

The cardiorespiratory system functions to extract oxygen from the atmosphere and deliver it to the tissues where it is required for aerobic metabolism. Alveolar ventilation is the volume of fresh gas each minute that reaches the alveoli and takes part in gas exchange. It is the first step in the oxygen cascade and the most important factor in determining the partial pressure of oxygen in the arterial blood (PaO_2). Alveolar ventilation is also responsible for the amount of CO_2 that is exhaled from the alveoli. In normal lungs, because carbon dioxide diffuses so readily across the alveolar capillary membrane, the alveolar CO_2 ($PACO_2$) is essentially equal to the arterial carbon dioxide tension ($PaCO_2$).

The oxygen cascade begins as oxygen enters the alveoli on inspiration (Fig. 8.1). Oxygen diffuses across the alveolar capillary membrane into the pulmonary capillary blood down a pressure gradient created by a pressure difference across the membrane. Diffusion is a passive process defined as the transfer of a gas from an area of higher pressure to an area of lower pressure. This diffusion of oxygen across the alveolar capillary membrane is accounted for by *Fick's first law of diffusion*, which asserts that the amount of gas diffusing through a membrane is *directly* proportional to the surface area available for diffusion but inversely proportional to the distance it has to diffuse. The diffusion capacity for the pulmonary vascular bed is optimal for achieving gas exchange because the membrane is exceedingly thin, and the surface area is

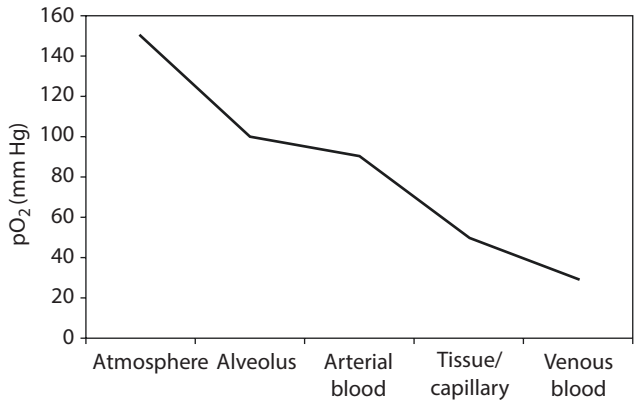

Fig. 8.1 The oxygen cascade

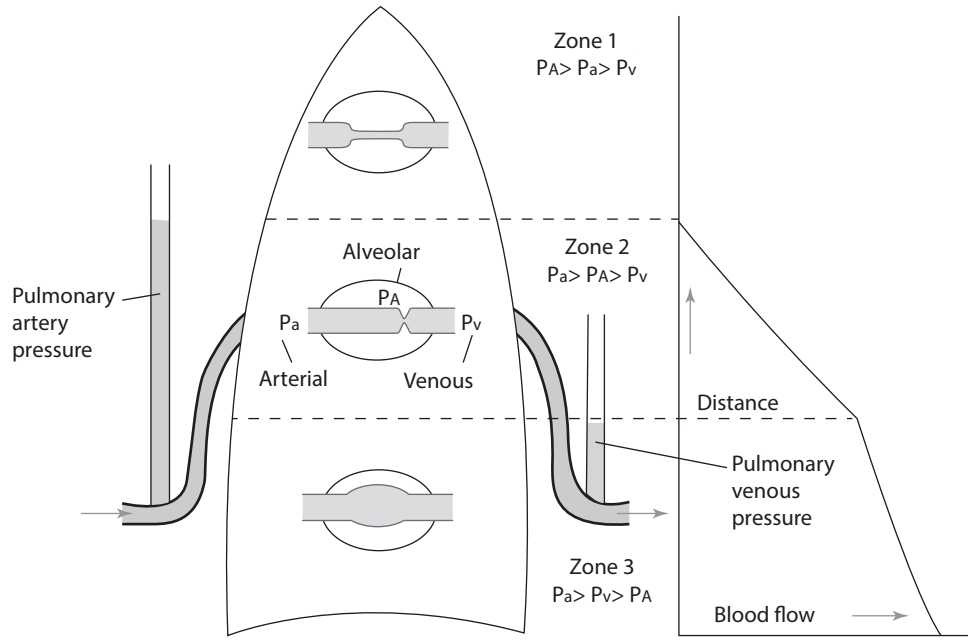

Fig. 8.2 West zones of pulmonary perfusion and ventilation. *Pa* arterial pressure, *PA* alveolar pressure, *Pv* venous pressure

vast due to the structure and arrangement of approximately 400 million alveoli. In addition, in the setting of increased O_2 demand, additional capillaries may be recruited which help to maintain adequate O_2 supply by decreasing diffusion distances.

The diffusion capacity for the pulmonary vascular bed is optimal for achieving gas exchange because the membrane is exceedingly thin, and the surface area is vast due to the structure and arrangement of approximately 400 million alveoli.

8.2.2 Distribution of Alveolar Ventilation

Both alveolar ventilation and perfusion pressures increase progressively from the apex of the lung to its base due to the effects of gravity. However, blood flow increases more rapidly than does ventilation. Therefore, the ventilation-perfusion (*V*/*Q*) ratio is highest at the apex of the lung and lower toward the base giving rise to what has come to be known as the West zones of perfusion and ventilation (Fig. 8.2). West described three theoretical zones of the lung from the apex to the base according to their relative distribution of ventilation and pulmonary blood flow. In Zone I, the least amount of blood flow occurs because alveolar pressure is greater than both pulmonary artery pressure and pulmonary venous pres-

sure. In Zone II, pulmonary arterial pressure is greater than alveolar pressure, and blood flow is determined by the difference between alveolar and arterial pressures independent of venous pressures. In Zone III, pulmonary arterial pressure exceeds pulmonary venous pressure which exceeds alveolar pressure. Consequently, flow is a function of both pulmonary arterial and venous pressures, and because pulmonary arterial pressure is higher, blood flow is down this gradient.

8.2.3 Carbon Dioxide Elimination

In general, blood holds more CO_2 than O_2, in part, because CO_2 is carried in three forms. Five to 10% of CO_2 is dissolved in the bloodstream, 5–20% is bound in the form of carbamino compounds, and the remainder (the vast majority) exists in the form of H_2CO_3.

Once oxygen reaches the bloodstream, it is delivered to the tissues where it is consumed in both the processes of cellular respiration and in a number of non-energy-producing oxidative reactions. During cellular respiration, which occurs in the mitochondria, oxygen is consumed generating energy in the form of adenosine triphosphate (ATP), with CO_2 being produced as a by-product. Alveolar ventilation is necessary to ultimately eliminate the CO_2 that is produced. Carbon dioxide exists in equilibrium with carbonic acid, H_2CO_3, a weak acid. Thus, the accumulation of carbon dioxide produces acidosis. In general, blood holds more CO_2 than oxygen, in part, because CO_2 is carried in three forms. Five to 10% of CO_2 is dissolved in the bloodstream, 5–20% is bound in the form of carbamino compounds, and the remainder (the vast majority) exists in the form of H_2CO_3. Carbon dioxide freely and efficiently diffuses from the tissues into the blood and then across the capillary alveolar membrane into the alveolar gas so that it can be eliminated through exhalation.

When CO_2 is not effectively eliminated by the lungs, hypercapnea results. In the face of hypercapnea, CO_2 freely diffuses into the cell, decreasing the intracellular pH by combining with H_2O to release H + as delineated in the following equation:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-.$$

The resulting acidemia initially triggers a sympathetic and adrenal response with endogenous catecholamine stimulation. Subsequently, the body has several compensatory mechanisms that are activated in order to surmount and counteract this acidosis.

1. Chemoreceptors in the brainstem and in the carotid body rapidly detect changes in the $PaCO_2$. In a spontaneously breathing, non-sedated patient with normal neuromuscular function, there is generally an initial increase in the minute ventilation in an attempt to increase carbon dioxide elimination and normalize the pH.
2. Deoxygenated hemoglobin molecules bind hydrogen ions as well as carbon dioxide to form carbaminohemoglobin in order to buffer the pH and prevent substantial changes in pH.
3. The kidneys increase the excretion of ammonium ion (NH_4^+) (thereby eliminating hydrogen ions) and chloride while retaining HCO_3^- and sodium (Na^+) after being exposed to hypercapnia for at least 6 h. The result is an increase in the plasma HCO_3^- concentration by approximately 3.5–4 mEq/L for every 10 mm Hg increase in the $PaCO_2$. The HCO_3^- then serves as a buffer for the existing free hydrogen ions.

8.2.4 Assessing Adequacy of Gas Exchange

Under normal conditions, the partial pressure of oxygen in the alveolus (PAO_2) is only slightly higher than that in the arterial blood (PaO_2), reflecting a nearly balanced equilibrium between the alveolar gas and the pulmonary capillary

blood. A significant gradient between the alveolar and arterial blood (A-a gradient) suggests a degree of lung injury causing a limitation of gas exchange. The composition of the alveolar gas depends on:

1. The oxygen content of both inspired air and the mixed venous blood
2. The quantity of air and blood reaching the alveoli
3. The ratio of alveolar ventilation to perfusion
4. The extent to which equilibrium is reached between the alveolar gas and the pulmonary capillary blood

While the arterial pO_2 is measured and reported in a blood gas analysis, it is more difficult to accurately measure the alveolar pO_2. The PAO_2 may be calculated from the following equation:

$$PAO_2 = PiO_2 - PaCO_2/RQ$$

where PiO_2 is the partial pressure of inspired oxygen and RQ is the respiratory quotient, the ratio of CO_2 produced to O_2 consumed in oxidative metabolism. The PiO_2 is determined by the atmospheric barometric pressure and the percent of oxygen being inspired. At sea level, where oxygen accounts for 21% of air, and atmospheric pressure is approximately 760 mm Hg, the partial pressure of inspired $O_2 = 760 \times 0.21$. However, that equation does not account for the displacement of oxygen and nitrogen by water vapor, which humidifies inspired air and thereby reduces the proportion of barometric pressure containing oxygen and nitrogen by 47 mm Hg. Therefore, the PiO_2 can be further defined by the following equation:

$$PiO_2 = \left(P_B - P_{H2O}\right) \times FiO_2 = 160\,\text{mm Hg}$$

At sea level, the PiO_2 will be approximately equal to 150 mm Hg (i.e., (760 mm Hg – 47 mm Hg) × 0.21 = 150 mm Hg). At altitude (e.g., on the top of Mount Everest, where the barometric pressure is 380 mm Hg), the PiO_2 will be significantly lower [e.g., (380 mm Hg – 47 mm Hg) × 0.21 = 70 mm Hg]. In hyperbaric oxygen chambers, where the barometric pressure is much higher than atmospheric, the PiO_2 will be higher.

The sum of the partial pressures of alveolar gases must equal ambient pressure. Therefore, an increase in one gas must result in a decrease in another. As gas moves down the airway into the alveolus, the partial pressure of oxygen is progressively reduced by the presence of carbon dioxide in the alveolar gas. The partial pressure of arterial carbon dioxide is utilized in the equation in place of alveolar carbon dioxide because carbon dioxide is so readily diffusible that arterial and alveolar carbon dioxide quickly equilibrate. However, to account for the fact that more oxygen is usually consumed than carbon dioxide is eliminated, this value is divided by the respiratory quotient. The respiratory quotient (RQ) is the ratio of the amount of CO_2 being produced and excreted to the amount of oxygen being consumed and utilized. It also reflects the oxidation of carbohydrates relative to fats. Under normal circumstances, the RQ approximates 0.8, but it can range between 0.67 and 1.3, depending on the clinical scenario and the relative composition of lipids (RQ = 0.7), carbohydrates (RQ = 1.0), and proteins (RQ = 0.8) being metabolized. Consequently, assuming a $PaCO_2$ of 40 mm Hg, a normal diet, and sea level barometric pressure, the PAO_2 is approximately 100 mm Hg.

$$PAO_2 = PiO_2 - PaCO_2 / RQ$$

$$PAO_2 = \left[\left(760\,\text{mm Hg} - 47\,\text{mm Hg}\right) \times 0.21\right] - 40\,\text{mm Hg} / 0.8$$

$$\left[\sim 150\,\text{mm Hg}\right] - 50\,\text{mm Hg} = \sim 100\,\text{mm Hg}$$

Under ideal conditions, the partial pressure of oxygen in the alveolus (P_AO_2) and in the arterial blood (PaO_2) should be nearly equal, and no gradient should exist, reflecting a balanced equilibrium between the alveolar gas and the pulmonary capillary blood. A significant gradient between the alveolar and arterial blood (A-a gradient) suggests a degree of lung injury causing a limitation of gas exchange.

The P_AO_2, may be calculated from the following equation:

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The PiO_2 is defined by the following equation:

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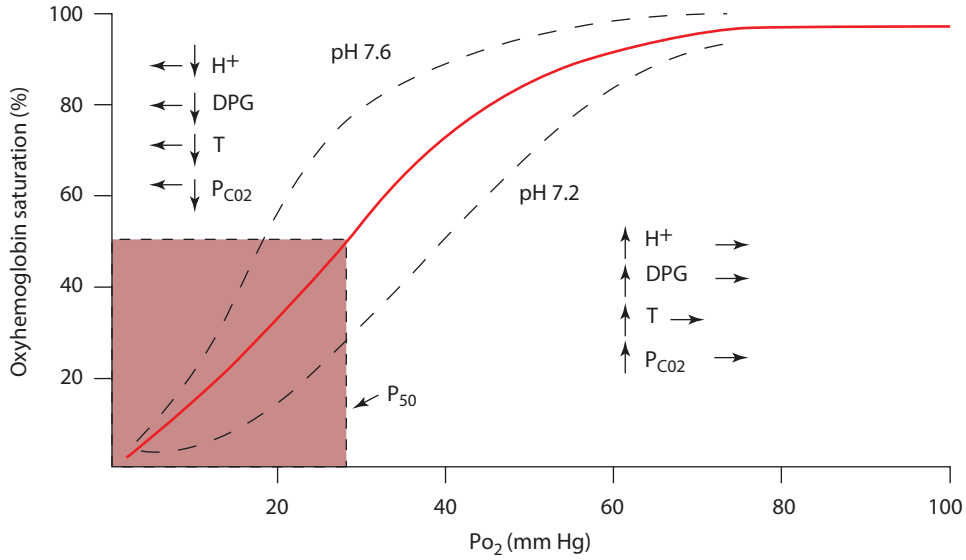

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Fig. 8.3 The oxygen-hemoglobin dissociation curve. *DPG* 2,3-diphosphoglycerate, *T* temperature

The PAO_2 is higher than the partial pressure of oxygen in the pulmonary artery and capillary blood, leading to the diffusion of oxygen from the alveoli into the bloodstream.

8.2.4.1 In the Bloodstream

In the bloodstream, oxygen molecules combine with hemoglobin to form oxyhemoglobin, the primary form in which oxygen is delivered to the tissues. The affinity that hemoglobin has for oxygen determines the degree of binding and the availability of oxygen for release to the tissues.

Several factors have been identified that influence the degree of binding of oxygen to hemoglobin. The oxygen-hemoglobin dissociation curve graphically depicts the relationship between the partial pressure of oxygen and the saturation of hemoglobin (Fig. 8.3). This graph describes the affinity of hemoglobin for oxygen and thus depicts the relative avidity of oxygen at the tissue level. The P_{50} is often used as a measure of this affinity. The P_{50} is defined as the PaO_2 at which hemoglobin is 50% saturated with oxygen. For normal adult hemoglobin (Hb A), the P_{50} is 27 mm Hg.

Various clinical conditions alter the affinity of hemoglobin for oxygen (Table 8.1). Conditions that produce a leftward shift of the curve as the result of an increase in the affinity of hemoglobin for oxygen have a lower P_{50} (a lower PaO_2 at which hemoglobin is 50% saturated with oxygen). This is most commonly seen with alkalosis and hypothermia. Hemoglobin F, the predominant form of hemoglobin in fetuses and neonates, has a lower P_{50} than hemoglobin A; therefore, the curve for hemoglobin F exists to the left of that of hemoglobin A. Conditions which cause a decrease in the affinity of hemoglobin for oxygen result in a higher P_{50} (a higher PaO_2 at which hemoglobin is 50% saturated with oxygen). These conditions cause a *rightward shift* of the oxygen-hemoglobin dissociation curve; common, clinically important examples include acidosis and hyperthermia.

The Bohr effect is a property of hemoglobin whereby its affinity for oxygen changes depending on the concentration of H+ or carbon dioxide. Increasing concentrations of H+ or carbon dioxide will reduce the affinity of hemoglobin

Table 8.1 Clinical factors that influence shifts in the oxygen-hemoglobin dissociation curve

Leftward shifts of the dissociation curve (increased oxygen affinity, lower P_{50})	Rightward shifts of the dissociation curve (decreased oxygen affinity, higher P_{50})
Decreased hydrogen ion (H^+) concentration	Increased hydrogen ion (H^+) concentration
Decreased RBC 2,3-diphosphoglycerate	Increased RBC 2,3-diphosphoglycerate
Decreased temperature	Increased temperature
Decreased partial pressure of carbon dioxide	Increased partial pressure of carbon dioxide
Increased pH	Decreased pH
Hemoglobin F (as compared to hemoglobin A)	

for oxygen. The Bohr effect provides part of the mechanism for the transfer of oxygen from the alveolus to the bloodstream and, subsequently, from the bloodstream to the tissues. In the lungs, the PCO_2 is low, and the pH is high. Under these conditions, the affinity of hemoglobin for oxygen is high, enhancing the uptake of oxygen from the alveoli into the bloodstream and on to the hemoglobin molecule in the red blood cell. By contrast, in the tissues, the high tissue PCO_2 and low pH favor the release of oxygen (Fig. 8.4). Similarly, the Haldane effect describes a property of hemoglobin whereby deoxygenated blood has an increased ability to carry carbon dioxide, and oxygenated blood has a decreased affinity for hydrogen ions and carbon dioxide. Therefore, in the lungs where oxygen is abundant, carbon dioxide is unloaded from the hemoglobin and made available to the alveolus for exhalation. Thus, the Bohr and Haldane effects represent molecular-level salutary enhancement of the already remarkable respiratory functions of hemoglobin.

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8.2.4.2 To the Tissues

From the pulmonary capillary blood, oxygen returns to the heart via the pulmonary veins. From there, oxygen travels in the systemic arterial blood, into the systemic capillaries, and, ultimately, into the mitochondria of the tissues. At each level of the oxygen cascade, the PO_2 progressively decreases until it reaches its clinically measurable nadir in the mixed venous blood returning to the heart. The PO_2 of mixed venous blood is determined by several factors, including the amount of oxygen delivered to the tissues (the oxygen supply), the amount of oxygen required by the tissues (the oxygen demand), and the capacity of the tissues to extract oxygen. If there is any impediment to oxygen delivery, organs will become deprived of oxygen. Oxygen consumption is defined by the following equations:

$$VO_2 = DO_2 \times O_2\text{extraction} = A - VDO_2 \times CO \times 10\,dL/L$$

where VO_2 is the oxygen consumption, DO_2 is the oxygen delivery, O_2 extraction is the fractional difference between arterial and venous O_2 content, the A-VDO_2 is the arteriovenous difference in oxygen content, and CO is the cardiac output.

$$\begin{aligned} DO_2\,\text{ml/min} &= CO\,\text{L/min} \times CaO_2\,\text{ml}\,O_2/\text{dL} \times 10\,\text{dL/L} \\ O_2\text{extraction} &= \left(1 - CvO_2/CaO_2\right) \\ \text{A-V}DO_2 &= \left(CaO_2 - CvO_2\right)\text{ml/dL} \\ 10\,\text{dL/L} &= \text{unit reconciliation} \end{aligned}$$

8.3 Mechanisms of Hypoxemia

Hypoxemia is a decrease in the oxygen content in the arterial blood reflecting a limitation of pulmonary gas exchange. There are four major causes of arterial hypoxemia: hypoventilation, ventilation-perfusion mismatch, shunted blood flow, and diffusion limitation.

Hypoxemia is a decrease in the oxygen content in the arterial blood reflecting a limitation of pulmonary gas exchange. The arterial oxygen content (CaO_2) is defined by the following equation:

$$CaO_2 = 1.34 \times Hb \times SaO_2 + 0.003 \times PaO_2$$

where 1.34 represents the oxygen combining capacity or the amount of oxygen in milliliters (mL) that a fully saturated gram of hemoglobin can carry, Hb represents the hemoglobin concentration in grams per deciliter, SaO_2 represents the arterial oxygen saturation of hemoglobin, and 0.003 represents solubility coefficient of oxygen in milliliters of oxygen in a deciliter of blood for each mm Hg partial pressure. The units for the arterial content of oxygen are milliliters of oxygen per deciliter of blood as mathematically illustrated below:

$$CaO_2\left(\text{mL}\,O_2/\text{dL}\right) = \frac{1.34\ \text{mL}\,O_2}{\text{g}} \times \frac{Hb\,\text{g}}{\text{dL}} \times SaO_2 + \frac{0.003\,\text{mL}\,O_2/\text{dL}}{\text{mm Hg}} \times PaO_2\,\text{mm Hg} = \frac{\text{mL}\,O_2}{\text{dL}}$$

Hypoxemia may therefore be the result of anemia or abnormalities of oxygenation. There are four major abnormalities of pulmonary gas exchange that may contribute to arterial hypoxemia: hypoventilation, ventilation-perfusion mismatch, shunted blood flow, and diffusion limitation.

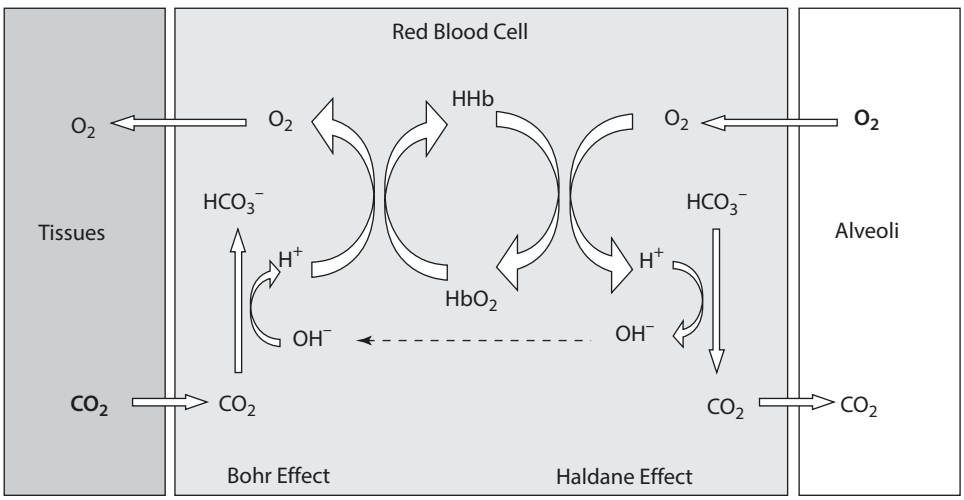


Fig. 8.4 The Bohr effect and the Haldane effect on oxygen transfer

8.3.1 Hypoventilation

Hypoventilation is an inadequate minute ventilation to maintain a normal $PaCO_2$ resulting in respiratory acidosis. Hypoventilation is not an oxygenation diffusion abnormality. Therefore, the A-a gradient usually does not increase. Rather, PAO_2 falls in accordance with the alveolar gas equation in response to increased $PACO_2$. The two main causes of hypoventilation are (1) *abnormal respiratory mechanics* causing increased airway resistance or decreased pulmonary compliance and (2) ventilatory control abnormalities such as ineffective muscles of respiration as in the case of neuromuscular disorders or *damaged neural sensing and signaling* as occurs in brain injury or deep sedation.

8.3.2 Ventilation-Perfusion Mismatch

The most common cause of hypoxemia is ventilation-perfusion mismatch. Gas exchange in the lung is best achieved when ventilation and perfusion are well matched. The degree to which ventilation matches perfusion determines how adequately gas exchange occurs. When alveolar ventilation matches pulmonary blood flow, carbon dioxide is appropriately eliminated, and the blood becomes fully saturated with oxygen. The ventilation-perfusion ratio can be determined using the following equation:

$$V/Q = \left[8.63 \times R\left(CaO_2 - CmvO_2\right)\right] / PACO_2$$

where V/Q represents the ratio of ventilation to pulmonary perfusion, 8.63 is a constant that reconciles the units and conventional conditions of expression, R is the respiratory exchange ratio, CaO_2 is the arterial content of oxygen, $CmvO_2$ is the mixed venous content of oxygen, and $PACO_2$ is the alveolar partial pressure of carbon dioxide.

When the V/Q ratio significantly exceeds one, ventilation is wasted because it does not participate in gas exchange. This is referred to as dead space ventilation. The most extreme example is the patient in cardiac arrest who is being ventilated but is no longer perfusing the lung. Anatomical dead space consists of the conducting airways (i.e., nasopharynx, trachea, subsegmental bronchi, terminal bronchioles) within which approximately 25% of each tidal volume is lost. Alveolar dead space consists of the alveoli not participating in gas exchange due to inadequate perfusion. The PCO_2 in these alveoli is relatively low since CO_2 is not added from the circulation. Physiological dead space is defined as the combination of both anatomical and alveolar dead space. The causes of increased dead space ventilation include tachypnea (anatomic dead space is fixed, thus rapid shallow breathing increases relative dead space), obstructive lung disease, and pulmonary emboli. The Bohr equation (not to be confused with the aforementioned Bohr effect) may be used to calculate the amount of physiological dead space:

$$V_d / V_t = \left(PaCO_2 - EtCO_2\right) / PaCO_2$$

V_d is the volume of dead space ventilation, V_t is the total ventilation volume, $PaCO_2$ is the arterial partial pressure of carbon dioxide, and $EtCO_2$ is the end tidal carbon dioxide.

As the V/Q ratio decreases below one, the PaO_2 decreases, and the $PaCO_2$ increases. When the V/Q ratio is less than one throughout the lung, hypoxemia is responsive to supplemental O_2. The normal compensatory response is

The Bohr equation may be used to calculate the amount of physiological dead space: $V_d/V_t = [PaCO_2 - EtCO_2]/PaCO_2$ where V_d is the volume of dead space ventilation, V_t is the total ventilation volume, $PaCO_2$ is the arterial partial pressure of carbon dioxide, and $EtCO_2$ is the end tidal carbon dioxide.

to increase the minute ventilation, producing either a low or normal $PaCO_2$. When ventilation ceases, the *V*/*Q* ratio reaches zero, and mixed venous blood enters the arterial circulation unchanged.

8.3.3 Shunting of Pulmonary Blood

A shunt is another cause of arterial hypoxemia. It can be thought of as the most extreme form of ventilation-perfusion mismatch where *V*/*Q* approaches zero. Shunts may occur at either the cardiac level with right to left intracardiac shunts or at the pulmonary level. The shunt fraction equation is

$$Q_s / Q_T = \left(CcO_2 - CaO_2\right) / \left(CcO_2 - CvO_2\right)$$

When the intrapulmonary shunt exceeds 30%, hypoxemia does not improve with supplemental oxygen because the shunted blood does not come in contact with enough of the high alveolar oxygen content.

where Q_s is the shunt blood flow, Q_T is the total blood flow, and the Cc, Ca, and Cv are the O_2 contents of the idealized alveolar capillary, measured arterial, and measured mixed venous blood, respectively. Under normal conditions, the percentage of intrapulmonary shunt is less than 10%. When the intrapulmonary shunt exceeds 30%, hypoxemia does not improve with supplemental oxygen because the shunted blood does not come in contact with enough of the high alveolar oxygen content. The PaO_2 levels fall proportionately to the degree of shunted blood flow.

8.3.4 Diffusion Limitation

A final, though infrequent, cause of arterial hypoxemia is diffusion limitation. Diffusion limitation occurs when there is disequilibrium between the partial pressure of a gas in the alveoli and the pulmonary capillaries causing an increase in the A-a gradient. Hypoxemia can occur due to a diffusion limitation because of a decreased driving force to push oxygen across the alveolar capillary membrane. Hypoxemia usually results when the diffusion capacity of the lung decreases to less than 50%. Increasing the FiO_2 may be enough to improve the driving pressure and enhance the transfer of oxygen from the alveoli into the blood. Most causes of decreased oxygen diffusion are caused by diffuse parenchymal lung diseases, which result in thickening of the alveolar capillary membrane. It has been estimated that blood passing through the lungs remains in a pulmonary capillary for only 0.75 s. Despite this brief time and a progressively decreasing alveolar capillary oxygen gradient (as the capillary blood becomes progressively more oxygenated), it has been estimated that pulmonary capillary blood approximates alveolar oxygen in only a third of this available time. This allows ample time for diffusion in clinical states of impaired perfusion.

8.4 Monitoring of Gas Exchange

8.4.1 Arterial Blood Gas Determination

An arterial blood gas (ABG) provides valuable data to help determine the acid-base status of a patient, the cause of any imbalance, as well as the degree of lung injury. Taken together, it is quite useful in assessing the adequacy of oxygenation and ventilation. The following parameters are provided in any ABG: pH, $PaCO_2$, PaO_2, HCO_3, and the base excess or deficit.

The pH describes whether acidemia or alkalemia is present. If the pH of the arterial blood is <7.35, then the patient is acidemic. If the pH of the arterial blood is >7.45, then the patient is alkalemic. The $PaCO_2$ is measured and may be used to determine the respiratory component of the pH. As a general rule, for every 10 mm Hg acute change in the $PaCO_2$, there is an inverse change of 0.08 pH units. Thus, accepting a $PaCO_2$ of 40 mm Hg and a pH of 7.40 as "normal" baselines, a patient with a $PaCO_2$ of 50 mm Hg should have a pH of 7.32 if the acid-base alteration is exclusively respiratory in origin. The $PaCO_2$ may also be used to determine the extent of dead space ventilation by the Bohr equation (as previously described):

As a general rule, for every 10 mm Hg acute change in the $PaCO_2$, there is an inverse change of 0.08 pH units.

$$V_d / V_t = \left(PaCO_2 - EtCO_2\right) / PaCO_2$$

In addition to assessing the respiratory component, the arterial blood gas can be used to assess the metabolic component of the acid-base alteration. Most blood gases provide a measurement of the bicarbonate concentration (either by direct measurement or determined from the measured pH and $PaCO_2$) and a calculated base excess or deficit. Because the carbon dioxide bicarbonate system accounts for only 75% of the buffering effect in the blood (the remainder being due to hemoglobin, phosphate, and plasma proteins), the base excess (or deficit) is a calculation used to compare the buffering capacity of the patient relative to normal. It is determined using the Siggaard-Andersen nomogram which relates pH, pCO_2, and HCO_3 while factoring in the contributions of the other blood buffers. There are equations to approximate the base excess (deficit) and its impact on pH that the pediatric critical care provider should understand. Specifically, the base excess can be approximated by the following equation:

$$\text{Base Excess} = \left(-1.2\right) \times \left(24 - \text{measured bicarbonate concentration}\right).$$

Moreover, for every change of 10 mEq/L in the base excess, there should be a 0.15 unit change in the pH. Conversely, for every 0.01 unit change in pH from expected, there will be a change of 0.67 mEq/L in the base excess.

This equation can be used in the interpretation of a blood gas to assess the metabolic component of an acid-base alteration. For example, a patient with a pH of 7.27 and a PCO_2 of 60 mm Hg should have a pH of 7.24 based solely on the respiratory component (carbon dioxide). This is based on the principle described above that every 10 mm Hg acute change from 40 mm Hg in the carbon dioxide should result in an inverse change of 0.08 in the pH. A $PaCO_2$ of 60 mm Hg is 20 mm Hg greater than 40 mm Hg, and consequently, the pH should be 0.016 less than 7.40, or 7.24. However, the pH in the example is 7.27. Remembering that for every change of 10 mEq/L in the base excess, there should be a 0.15 unit change in the pH, it can be stated that for every 0.01 change in pH from expected, there will be a corresponding 0.67 change in the base excess. In the example described above, the pH is 0.03 pH units higher than the expected pH based on the respiratory component alone. Since there is a 0.67 change in the base excess for every 0.01 change in the pH, the base excess in this patient would be $3 \times 0.67 = +2$. This would suggest that the patient has some metabolic compensation for his respiratory acidosis. Most simply stated, the base excess (or deficit) roughly quantifies the change in pH not accounted for by any change in $PaCO_2$.

For every change of 10 mEq/L in the base excess, there should be a 0.15 unit change in the pH.

The PaO_2 is also measured in the arterial blood gas and provides useful data reflecting the degree of hypoxia. The PaO_2 is utilized in a number of equations assessing the degree of lung injury. For example, the PaO_2 is utilized in the A-a gradient equation:

$$\text{A - a gradient} = PAO_2 - PaO_2$$
$$= \left[PiO_2 - PaCO_2 / RQ\right] - PaO_2$$
$$= \left[\left(\left(P_{BAR} - P_{H_2O}\right) \times FiO_2\right) - PaCO_2 / RQ\right] - PaO_2$$

The oxygen index (OI) is a marker of lung injury and is determined by the equation [(Mean airway pressure * FiO_2)*100] / PaO_2.

In addition, the PaO_2 is also used in determining the oxygen index (OI):

$$\frac{\left(\text{Mean airway pressure} \times FiO_2\right) \times 100}{PaO_2}$$

The OI has been used in a number of studies as a means to quantify and compare the degree of lung injury. It can be thought of as the magnitude of potentially injurious therapeutic interventions to the alveoli (pressure and fraction of inspired oxygen) over the result (the partial pressure of arterial oxygen achieved from delivering such interventions). As therapy (the numerator) increases to treat a declining PaO_2 in the denominator, the OI rises, indicating more severe lung injury.

The PaO_2 can also be used to determine the ratio of the partial pressure of oxygen and the fraction of inspired oxygen (P/F ratio). This P/F ratio has also been used extensively in both clinical and research work. In fact, the P/F ratio has been incorporated into the definitions of severity of acute respiratory distress syndrome (ARDS). In the Berlin definitions, P/F ratio > 200 and ≤300 mm Hg is considered mild ARDS, P/F ratio >100 and ≤200 is considered moderate ARDS, and P/F ratio ≤100 is considered severe ARDS. In contrast to the OI, the P/F ratio does not incorporate mean airway pressure and, therefore, can be utilized to assess the degree of lung injury in non-intubated patients. Although useful for that reason in the non-intubated patient, it may provide misleading assessments in patients receiving positive pressure ventilation. Since the P/F ratio often improves with increasing mean airway pressure, using it alone as an index of severity of lung disease will be misleading. An improved P/F ratio in response to the application of higher mean airway pressure does not mean that the patient has less lung injury. The oxygenation index, on the other hand, accounts for the increase in mean airway pressure, thereby balancing the improvement in PaO_2 which would itself decrease the calculated OI. The OI, and variations utilizing oxygen saturation in lieu of PaO_2, is the preferred severity grading tool for pediatric acute respiratory distress syndrome (PARDS) (▶ Chap. 11).

8.4.2 Pulse Oximetry

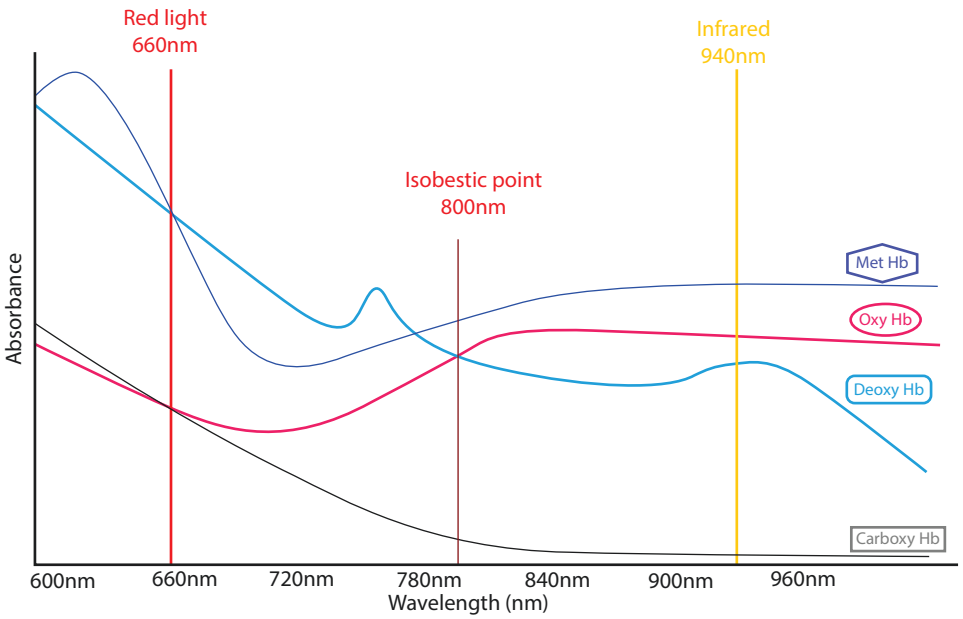
The use of pulse oximetry has become universally accepted for providing instantaneous information regarding the oxygen saturation of arterial blood. This technology is based on the light absorption characteristics of different forms of hemoglobin and utilizes two principles. First, the attenuation of light passing through tissues changes with the pulsation of arterial blood, and second, the degree of attenuation is based on the composition of the arterial blood. Present-day pulse oximeters utilize two wavelengths of light, visible red (660 nm) and near-infrared (900–940 nm), to discriminate between oxyhemoglobin and deoxyhemoglobin. Oxygenated hemoglobin reflects red light much better than other hemoglobin species resulting in the much "redder" appearance of oxygenated blood. As arterial blood is pumped through a tissue bed, the absorption of light changes in a pulsatile manner. The light absorption of the tissues, the venous blood, and the capillary blood does not change. Therefore, the degree of light absorption from these components can be subtracted from

the total light absorption to yield the amount of light absorption of the arterial blood alone. Because the absorption of light in the near-infrared range is relatively constant over a wide range of oxygen saturations, changes in the absorption at the 660 nm wavelength of the arterial blood reflect oxygenation and can be referenced to the near-infrared absorption. In this way, the arterial blood oxygen saturation may be determined using predetermined algorithms.

The ratio of the oxygen saturation ascertained from pulse oximetry to the fraction of inspired oxygen (the S/F ratio) is now being used in lieu of the P/F ratio as a marker of lung injury, in risk stratification, and for research purposes. Although there are limitations to this application, the S/F ratio may be beneficial for use in children with acute hypoxic lung injury, as it is a noninvasive measurement.

Pulse oximetry has been found to be very accurate for oxygen saturations greater than 70% with confidence limits of 2–4%. However, for saturations below 70%, the accuracy is substantially less. Moreover, there are clear limitations to the use of pulse oximetry. Motion artifact is probably the most common example of erroneous data being generated by pulse oximetry. This is easily recognized and often results in frequent triggering of the oximeter alarms. Pulse oximeters have been developed that attempt to minimize the effect of motion artifact. In addition, environmental light may interfere with pulse oximetry accuracy. Although this has not been found to be applicable to all oximeters, shielding the pulse oximeter probe from external light may result in improved performance. Other limitations of pulse oximetry include any factor that might interfere with the ability to detect and monitor a pulse such as hypoperfusion, vasoconstriction, and hypothermia. In these circumstances, the pulse oximeter will often not record at all or display an inaccurate reading.

In addition to the potential for error described above, clinical situations in which hemoglobin binds to substances other than oxygen may also result in erroneous pulse oximetry values. For example, in the setting of carbon monoxide poisoning, hemoglobin binds with great affinity to carbon monoxide to form carboxyhemoglobin. As can be seen in ◘ Fig. 8.5, carboxyhemoglobin has a very similar light absorption as oxyhemoglobin at 660 nm. Consequently, The pulse oximeter inappropriately interprets carboxyhemoglobin to be oxyhemoglobin and, therefore, overestimates the true oxygen saturation of hemoglobin in the setting of carbon monoxide poisoning.



◘ **Fig. 8.5** Light absorbance characteristics of various forms of hemoglobin

the pulse oximeter will inappropriately interpret carboxyhemoglobin to be oxyhemoglobin and, thereby, overestimate the true oxygen saturation of the hemoglobin. This may occur in the setting of significant hemolysis where significant amounts of carbon monoxide are formed and bind to hemoglobin to form carboxyhemoglobin. In the setting of carboxyhemoglobinemia, blood gas analysis with co-oximetry, which measures other forms of hemoglobin (carboxyhemoglobin, methemoglobin, oxyhemoglobin, deoxyhemoglobin), is necessary to truly ascertain the oxygen saturation of the blood.

The situation is different in the setting of methemoglobinemia. Initially, as methemoglobin levels increase, the pulse oximetry saturation will decrease to 80–85%. However, because methemoglobin adsorbs light equally well at 660 and 940 nm, the absorbance of light in pulsatile blood and baseline nonpulsatile reference tissue will increase at an equal pace. The ratio between the two points of light absorbance will be one resulting in a displayed oxygen saturation of approximately 85%. Consequently, even with further increases in the methemoglobin, the pulse oximeter saturation reading will remain approximately 85%. As with carboxyhemoglobinemia, blood gas analysis with co-oximetry is necessary in the setting of methemoglobinemia to accurately determine the percentage of oxyhemoglobin.

Finally, pulse oximetry may not be completely accurate in the setting of high concentrations of sickle hemoglobin (hemoglobin S). In addition to the abnormal shape of sickled red blood cells that potentially alter the normal absorption of light, a rightward shift of the oxygen-hemoglobin dissociation curve may result in lower pulse oximeter readings for any given partial pressure of arterial oxygen. In addition, significant hemolysis associated with sickle cell disease may result in carboxyhemoglobinemia and erroneous pulse oximeter values as described above.

8.4.3 Capnometry

Capnometry has become a standard of care to confirm appropriate endotracheal intubation.

Capnometry is the measurement of carbon dioxide in expired gas. Capnometers measure carbon dioxide using one of two techniques, each with its own advantages and disadvantages. The more common form of capnometry in intubated patients is referred to as mainstream. The mainstream capnometer is placed in line with the endotracheal tube circuit. It utilizes a light-emitting detector that is positioned on either side of an airway adaptor attached to the top of the endotracheal tube. It uses infrared light absorbance to detect carbon dioxide. Because of its in-line positioning, it allows for rapid breath-to-breath analysis of carbon dioxide. Although it does not depend on the aspiration of gas, it is susceptible to interference by respiratory secretions or humidity. Moreover, because of the need of an adaptor, additional dead space is added to the circuit. This is usually not problematic except in the smallest of infants. Finally, the sensor used by some mainstream capnometers may be large and heavy relative to the endotracheal tube and, thus, may place undue tension on the tube.

Sidestream sampling is the other form of capnometry. It is less commonly used in intubated patients but is increasingly being utilized in non-intubated circumstances. The sidestream technique continuously aspirates a small amount of gas as the patient ventilates either spontaneously or through a ventilator circuit. The advantage of this method is that the apparatus adds no additional dead space or weight to an endotracheal tube. The disadvantage, particularly in smaller patients, is that it may decrease minute ventilation due to the aspiration of gas. Also, because of the method of sampling, mucous and water may be inadvertently aspirated into the monitoring device obstructing optimal gas

flow. Finally, because the gas has to be pulled out of the endotracheal tube/ventilator circuitry, there is a delay in the response time to changes in carbon dioxide. It should be noted, however, that some gas aspirating systems utilize an adapter positioned between the ventilator circuit and the endotracheal tube, adding to system dead space similar to mainstream capnometers.

Capnometry has become an important component of pediatric critical care monitoring. First, and perhaps foremost, it has become a standard of care to confirm correct placement of an endotracheal tube after intubation. This may be accomplished in one of two ways. The simplest involves attaching the endotracheal tube to a colorimetric capnometer that will change colors when exposed to carbon dioxide, usually from purple to yellow. The colorimetric capnometers contain a disc that when exposed to carbon dioxide produces hydrogen ions. The increase in hydrogen ions and the resultant change in pH result in the color change of the disc. If no carbon dioxide is detected, the colorimetric capnometer will remain purple. If carbon dioxide is detected, the disc will change color from purple to yellow. This method may only be used for short-term confirmation of exhaled carbon dioxide. The second method involves graphically displaying the detected level of carbon dioxide. The second method, capnography, may be used to quantify the amount of carbon dioxide detected and may reflect the level of carbon dioxide at any given point in the respiratory cycle.

There are situations in which capnometry/capnography may provide misleading information regarding the appropriate positioning of an endotracheal tube. Tube placement above the vocal cords in the hypopharynx may allow for sufficient ventilation such that carbon dioxide may be detected despite the tube not being positioned in the trachea. In contrast, in the setting of cardiac arrest or extreme hypoperfusion, carbon dioxide may not be delivered to the lungs, resulting in little to no carbon dioxide in the exhaled breaths. Consequently, the capnometer/capnograph will not detect carbon dioxide even though the endotracheal tube may be properly positioned in the trachea. Large air leaks around the endotracheal tube or obstructed tubes may also result in diminished amounts of carbon dioxide being detected despite appropriate positioning of the endotracheal tube. It is recommended that capnometry/capnography be assessed over at least the first six breaths of ventilation to minimize the risk of misinterpretation.

In addition to confirming endotracheal intubation, capnometry may be used to monitor arterial carbon dioxide content noninvasively. Carbon dioxide readily diffuses across the alveolar capillary membrane such that the concentrations of arterial and alveolar carbon dioxide quickly equilibrate. Consequently, the partial pressure of carbon dioxide in the alveolus closely approximates the partial pressure of carbon dioxide in the arterial blood. Leaving the alveolus, gas is exhaled by traversing a terminal bronchiole, a subsegmental bronchus, a main bronchus, the trachea, the endotracheal tube, and into the expiratory limb of the ventilator circuit. During that entire transit, which is essentially dead space, very little additional gas exchange occurs. Consequently, under ideal circumstances, by measuring the peak concentration of carbon dioxide (end tidal) as it exits the endotracheal tube or nasopharynx, it is possible to estimate the concentration of carbon dioxide in the alveolus and, therefore, the partial pressure of carbon dioxide in the arterial blood. This is the foundation upon which the development of capnometry was developed. In the patient without cardiopulmonary disease, the system works well, and exhaled end tidal carbon dioxide approximates $PaCO_2$. In fact, the end tidal carbon dioxide is usually 2–5 mm Hg lower than the $PaCO_2$ because of anatomic dead space ventilation and the expected, mild ventilation-perfusion mismatch in the upper

Under ideal circumstances, by measuring the peak concentration of carbon dioxide (end tidal) as it exits the endotracheal tube or nasopharynx, it is possible to estimate the concentration of carbon dioxide in the alveolus and, therefore, the partial pressure of carbon dioxide in the arterial blood.

lung fields (West Zone I). In those upper lung fields, ventilation is slightly greater than perfusion because of the gravitational forces favoring blood flow to the lower, more dependent lung fields (see Fig. 8.2).

As the end tidal carbon dioxide ($EtCO_2$) represents the average partial pressure of ventilated alveoli and the $PaCO_2$ represents the same for perfused alveoli, any alteration in ventilation-perfusion matching will result in an inaccurate $EtCO_2$ estimate of the $PaCO_2$.

However, as might be anticipated, there are many clinical situations common to the pediatric intensive care unit where the premise of balanced ventilation and perfusion is invalid; thus, capnometry no longer provides reliable estimates of arterial carbon dioxide. As the end tidal carbon dioxide ($EtCO_2$) represents the average partial pressure of ventilated alveoli and the $PaCO_2$ represents the same for perfused alveoli, any alteration in ventilation-perfusion matching will result in an inaccurate $EtCO_2$ estimate of the $PaCO_2$. For example, in any setting of an increased ventilation to perfusion ratio (e.g., increased dead space secondary to decreased cardiac output, pulmonary embolus), the $EtCO_2$ will underestimate the $PaCO_2$. For example, if the $PaCO_2$ is 40 mm Hg, and only half of the alveoli are being effectively perfused, the carbon dioxide coming out of the perfused alveoli will be 40 mm Hg. However, if the other 50% of alveoli are not being perfused at all, the carbon dioxide coming out of these alveoli would be zero. When the gas from the two sets of alveoli meet and mix in the trachea, the resulting concentration of carbon dioxide detected at the capnometer would be 20 mm Hg (as opposed to the true arterial value of 40 mm Hg).

Capnography may be used to estimate the percentage of dead space ventilation.

In light of this, end tidal carbon dioxide monitoring is being utilized as a method to help assess adequacy of cardiac output, chest compressions, and pulmonary perfusion during cardiopulmonary resuscitation, as well as minimizing the chance of potentially deleterious hyperventilation. Although PALS Guidelines have recommended improving CPR quality if $ETCO_2$ levels are consistently less than 15 mm Hg, a specific value at which to maintain the $ETCO_2$ for optimal outcomes has not been uniformly defined. What does seem to be evident in recent studies is that attempting to maintain higher end tidal carbon dioxide levels does seem to be associated with better outcomes. Similarly, but conversely, in the setting of a decreased ventilation-perfusion ratio, where alveoli are being perfused, but not ventilated, the carbon dioxide in these non-ventilated alveoli will never be detected by the capnometer. Therefore, the $EtCO_2$ detected by capnometry will reflect only those alveoli that are actively participating in ventilation.

In addition to the absolute numbers provided by the capnogram, the waveform may also be used to detect problems within the cardiopulmonary system. A normal capnogram consists of four stages (Fig. 8.6a). First, there is an inspiratory baseline (I) where atmospheric air at the sensor has little to no carbon dioxide thereby providing a baseline value of zero. Once exhalation begins, and the air from the anatomic dead space is cleared (no or minimal carbon dioxide present), the second stage is characterized by a rapid rise (steep) in the measured carbon dioxide as alveolar air rich with carbon dioxide rushes past the sensor (III). During exhalation, the concentration of carbon dioxide quickly stabilizes, and the level of carbon dioxide roughly flattens. The highest recorded value of carbon dioxide at the end of exhalation is recorded as the end tidal carbon dioxide. During the final stage of the respiratory cycle, inspiration occurs. With the fresh rush of carbon dioxide-free air across the sensor, the carbon dioxide level quickly plummets to zero (IV). Monitoring of the capnogram allows for the continuous monitoring of airway obstruction, apnea, hypercarbia, and return of spontaneous circulation (Fig. 8.6b–d). It also allows for a more exact measurement of the respiratory rate than traditional thoracic impedance devices. The capnogram waveform may also be used to detect conditions associated with increased airway resistance. For example, waveforms associated with a wider angle between the upslope and the plateau

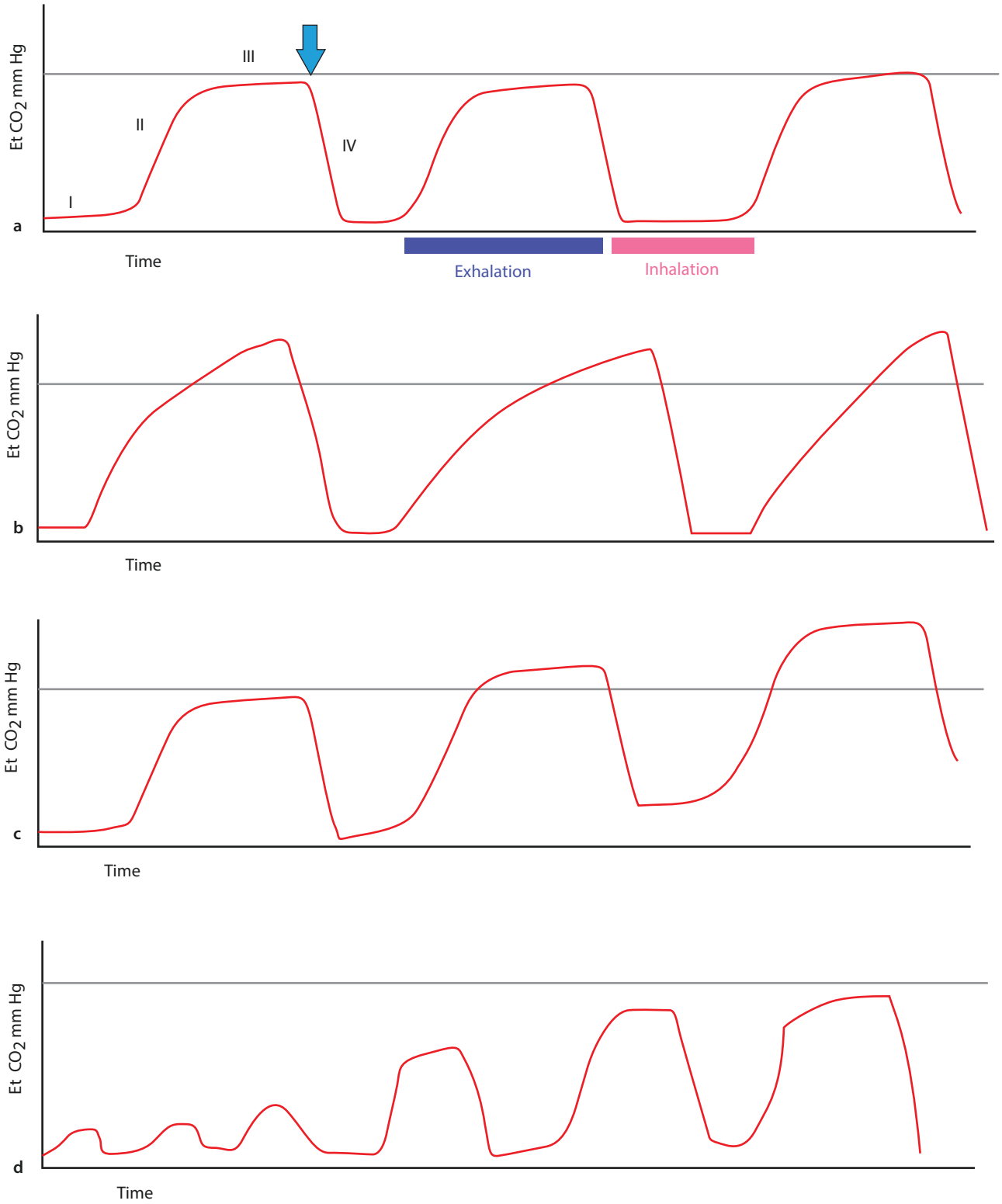


Fig. 8.6 **a** A normal capnogram consists of four stages: I. Inspiratory baseline where atmospheric air at the sensor has little to no carbon dioxide thereby providing a baseline value of zero. II. Start of exhalation and rapid rise in the measured carbon dioxide as alveolar air rich with carbon dioxide rushes past the sensor. III. Plateau phase where the concentration of carbon dioxide quickly stabilizes and the level of carbon dioxide roughly flattens. The highest recorded value of carbon dioxide at the end of exhalation is recorded as the end tidal carbon dioxide (arrow). IV. During the final stage of the respiratory cycle, inspiration begins, and the carbon dioxide level quickly returns to zero. **b** Capnogram demonstrating exhalatory obstruction as seen in bronchospasm ("shark fin capnogram"). **c** Capnogram demonstrating carbon dioxide rebreathing as would be seen in insufficient expiratory time or with a blocked exhalatory valve. **d** Capnogram during CPR demonstrating return to spontaneous circulation

stages of exhalation suggest slower carbon dioxide removal and increased airway resistance. The same is true for an uptrending stage III plateau.

Capnography is also useful for the monitoring of the non-intubated patient to monitor the respiratory status in the setting of seizures, altered mental status, overdoses, and particularly in the setting of procedural sedation. Because the medications required for such sedation may be associated with respiratory compromise, close monitoring of the respiratory system is of paramount importance. Traditionally, oxygenation has been monitored with pulse oximetry, and ventilation has been assessed with clinical observation alone. Sidestream capnography, by means of a nasal oral cannula which simultaneously monitors exhaled carbon dioxide and delivers low flow oxygen, allows for a more precise and detailed assessment.

8.4.4 Transcutaneous Oxygen and CO_2 Monitoring

The monitoring and trending of oxygen and carbon dioxide can also be accomplished using transcutaneous technology. This technology has been used since the late 1970s and the early 1980s and has largely been replaced by newer, more reliable technology (described above) which has overcome some of the limitations of transcutaneous monitoring. The use of the transcutaneous technology requires warming of the skin to promote hyperperfusion allowing the monitors to electrochemically detect O_2 and CO_2 levels. In this way, frequent blood draws are avoided, and a mode of continuous monitoring is achieved. The limitations, however, prevent practical regular and reliable use. The electrodes frequently need to be recalibrated; the measurement is inaccurate when the skin is not optimally perfused, as in the case of edema, acidosis, shock, or hypothermia. Furthermore, in order to achieve hyperperfusion, the skin is warmed, and burns have been reported. Finally, the response time is much slower than with the other noninvasive techniques described above. The clinical scenario in which transcutaneous CO_2 monitoring may be of particular benefit is in the child on high-frequency oscillatory ventilation in which end tidal CO_2 monitoring is not possible. Transcutaneous O_2 monitoring has been utilized to monitor the adequacy of tissue perfusion following vascular surgery.

8.5 Summary

The effective transfer of oxygen from the atmosphere into the body and ultimately to the various tissues is essential to maintaining life, as is the efficient transfer of carbon dioxide from the body to the environment. The exchange of these gases occurs via a series of complicated physiological processes. Abnormalities in the effective transfer of oxygen from the atmosphere into the bloodstream have been categorized into four pathophysiological mechanisms: hypoventilation, ventilation-perfusion mismatch, intrapulmonary shunt, and diffusion limitation. An understanding of each of these pathophysiological processes will facilitate therapeutic interventions to improve oxygenation. Moreover, close monitoring of the status of gas exchange is essential for the care of critically ill children. Both invasive and noninvasive methods exist to effectively monitor gas exchange in children. A clear understanding of these techniques will foster effective management of critically ill children with impaired gas exchange.

Review Questions

1. You arrive to a code for a child in septic shock who has just experienced a cardiac arrest. The code has been going on for ~10 min without return of spontaneous circulation. He has been intubated and is being ventilated at a rate of 8 bpm. Chest compressions are ongoing. The most helpful reason to request that an end tidal CO_2 monitor is placed at this time is:
   A. To have an objective way to estimate the efficacy of chest compressions by estimating pulmonary perfusion
   B. To avoid having to perform an arterial puncture
   C. To better assess the degree of airway restriction
   D. To be able to detect when the spontaneous respirations resume
   E. To assess the degree of acidosis and therefore need for administration of sodium bicarbonate administration

2. Intrapulmonary shunt
   A. Is the most severe form of dead space ventilation.
   B. Occurs when the ratio of ventilation to perfusion of lung units approaches infinity.
   C. Is the quotient of the difference in the idealized alveolar capillary O_2 content and the measured arterial O_2 content and the difference in the idealized alveolar capillary O_2 content and the measured mixed venous O_2 content.
   D. Under normal conditions the percentage of intrapulmonary shunt is >10%.
   E. In excess of 30% can only be overcome by administering 100% FiO_2.

3. A 15-month-old is admitted to the PICU with acute respiratory failure with bronchiolitis secondary to rhinovirus. What objective data can you obtain that may help you in risk stratification in determining the likelihood of requiring intubation?
   A. Respiratory rate
   B. Degree of wheezing
   C. Procalcitonin level
   D. SaO_2/FiO_2 ratio
   E. Time of last meal

4. A 10-year-old girl is in acute hypoxemic respiratory failure and is being managed with conventional invasive ventilation. O_2 saturation is 90% on an FiO_2 of 60% and a PEEP of 10 cm H_2O. Peak inspiratory pressure is 35 cm H_2O. Mean airway pressure is 18 cm H_2O, and $EtCO_2$ is reading 45 with a ventilator rate of 22 breaths per minute.
   You are debating whether to place an arterial catheter and decide that it would be helpful for the following reason:
   A. It allows you to measure the PaO_2 which is the only way to calculate the partial pressure of O_2 in the alveoli.
   B. The more data that helps drive patient care, regardless of invasiveness, the better the long-term outcome for the patient.
   C. It will enable you to calculate an oxygenation index which will help you prognosticate likelihood of survival.
   D. The continuous blood pressure measurement will help you mitigate against barotrauma.
   E. It will allow you to obtain a PaO_2 which can be utilized to help you trend the degree of lung injury.

5. A 2-year-old male is admitted with uncompensated shock. He is tachypneic, tachycardic, and hypotensive and had 90% O_2 saturation on RA. His labs are significant for a lactic acidosis. Which of the following statements explain his hypoxemia despite absence of lung disease?
   A. The elevated CO_2 levels in his blood are causing the tachypnea and therefore increasing the oxygen affinity of his hemoglobin molecules.
   B. His acidotic state has caused a rightward shift of the oxygen-hemoglobin dissociation curve causing his hemoglobin molecules to have a lower affinity for O_2.
   C. He still has a predominance of hemoglobin F.
   D. He has become hypothermic slowing his metabolic rate and improving the efficiency of O_2 delivery.
   E. His tachycardia is ensuring adequate pulmonary blood flow.

Answers

1. A
2. C
3. D
4. E
5. B

Suggested Readings

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Upper Airway Obstruction

Steven E. Lucking

Contents

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Learning Objectives

- Describe the anatomic differences in the airway of a child as compared to an adult
- Recognize the signs and symptoms of a child with upper airway obstruction
- Understand the approach to safe diagnostic evaluation of the infant or child with upper airway obstruction
- Understand the differential diagnosis of a child with upper airway obstruction in the context of age at presentation, congenital versus acquired, and chronic versus acute
- List and describe clinical differences in infectious etiologies of acute upper airway obstruction
- Understand the approach to stabilization and management of the child with upper airway obstruction
- Know the mechanism of action of the major therapies aimed at treatment of upper airway obstruction
- Know the indications for endotracheal intubation (including a clinical plan for intubation) and tracheostomy in a child with upper airway obstruction
- Outline a plan for the child with upper airway obstruction with an "unintubatable" airway (including laryngeal mask airway and cricothyroidotomy)

9.1 Introduction

The degree of airway obstruction is not proportionate to the amplitude of the stridor. Severe obstruction with poor airflow may occur with minimal stridor.

Acute upper airway obstruction presents an immediate threat to life. Following loss of the upper airway, hypoxemia with resultant cardiac arrest and death can ensue within minutes. Inspiratory stridor, a harsh, usually high-pitched sound, is the hallmark of upper airway obstruction. However, upper airway obstruction cannot occur in the absence of stridor, because profound degrees of obstruction may manifest silently if airflow is nearly absent. When confronted with a child who has acute upper airway obstruction, the practitioner must assess the degree of obstruction quickly and accurately. The possibility of progression to complete airway obstruction with hypoxemia and cardiac arrest must be appreciated. Delaying intervention in a child whose airway is unstable may be costly, but unnecessary instrumentation in a child who has stable upper airway obstruction may precipitate a crisis.

9.2 Anatomic and Physiologic Considerations

The extrathoracic upper airways are narrower during inspiration due to the relatively lower (negative relative to atmospheric) pressure within the lumen as air is being drawn through by the actions of the respiratory muscles. This lower luminal pressure in combination with the highly compliant nature of upper airway tissue creates a predilection toward inspiratory obstruction; this is especially true in infants. Pressure within the extrathoracic upper airways varies from mildly positive relative to atmospheric during quiet expiration to markedly greater than atmospheric during forced expiration. Thus, the internal diameter of extrathoracic airways is augmented somewhat during expiration, lessening the obstruction. Hence, airflow limitation from upper airway narrowing is greater during inspiration, and symptoms are apparent predominantly during inspiration.

The predominance of expiratory sounds suggests obstruction at the level of the intrathoracic trachea or lower airways.

Stridor is primarily, though not exclusively, an inspiratory phenomenon. The presence of mainly expiratory symptoms, regardless of the acoustic nature of the sound, should warn one to the presence of airway obstruction at the level of the intrathoracic (lower trachea and distal) airways. One exception is

the behavior of dynamic subglottic lesions, such as a soft subglottic cyst, which may move upward against the undersurface of the glottis causing expiratory noise but fall away from the glottis with no inspiratory sound.

The narrowest point of the airway of an infant or small child is at the level of the cricoid ring. This results in a funnel shape to the glottis and subglottic area. In contrast, the narrowest part of the airway of an older child or adult is vocal cord opening. There is no circumferentially narrow area of the adult upper airway which would correspond to the cricoid ring in the small child. Because of the fourth-power relationship between airway diameter and airway resistance (Poiseuille equation for nonturbulent flow), the same amount of airway encroachment or edema in millimeters causes a far greater physiological obstruction in a small child than in an adult. In addition, airways affected by edema may change flow dynamics from laminar to turbulent which is especially important at high flow rates and at locations where the diameter or angle of the airway changes abruptly. The pressure gradient to support turbulent flow is proportional to the square of the gas flow rate (as opposed to the first order with laminar flow) and is also proportionate to gas density. This effect of gas density on flow dynamics in the presence of turbulent flow is the rationale for the use of helium-oxygen gas mixtures in the treatment of some forms of upper airway obstruction.

In the absence of hypoxemia, a previously healthy infant or child can tolerate significant degrees of hypercapnia without organ damage.

The cause of death in patients who have airway obstruction is progressive hypoxemia and cardiac arrest. The oxygen consumption of a small child, approximately 7 ml/kg/min, is much greater than that of an adult (3 ml/kg/min) relative to body size. The progression to irreversible organ injury in the face of hypoxemia may be more rapid than for the adult. Thus, the immediate concern when first assessing the child is to provide oxygen and assess the degree of oxygen saturation. Carbon dioxide retention is a secondary concern relative to hypoxemia. An otherwise healthy infant or child can tolerate significant degrees of hypercapnia without organ damage. In addition, the degree of hypercapnia can vary over a matter of minutes as a result of factors such as the child's level of agitation, the degree of airway obstruction, the response to palliative therapies, and the onset of fatigue. For these reasons, arterial blood gas (ABG) measurement, which provides an assessment of pH and $PaCO_2$ for but one moment in time, generally is not considered sufficiently worthwhile, as the amount of distress it causes the child has the real potential to worsen the degree of airway obstruction for the reasons stated above. However, pulse oximetry monitoring is an extremely valuable objective assessment and is required except in rare cases where the probe placement worsens the symptoms due to agitation.

9.3 Differential Diagnosis of Upper Airway Obstruction

For the purpose of offering a diagnostic framework, the causes of upper airway obstruction have been divided into three categories: those occurring in early infancy secondary to congenital, developmental, or birth events; those acquired later in childhood from infectious etiologies; and those acquired later in childhood from noninfectious causes.

9.3.1 Early Infancy

Laryngomalacia is the single most common cause of stridor that begins in early infancy.

Congenital abnormalities of the airway may manifest with airway obstruction and stridor starting early in infancy and occasionally in the immediate newborn period (◘ Fig. 9.1) *Laryngomalacia* is the single most common cause of

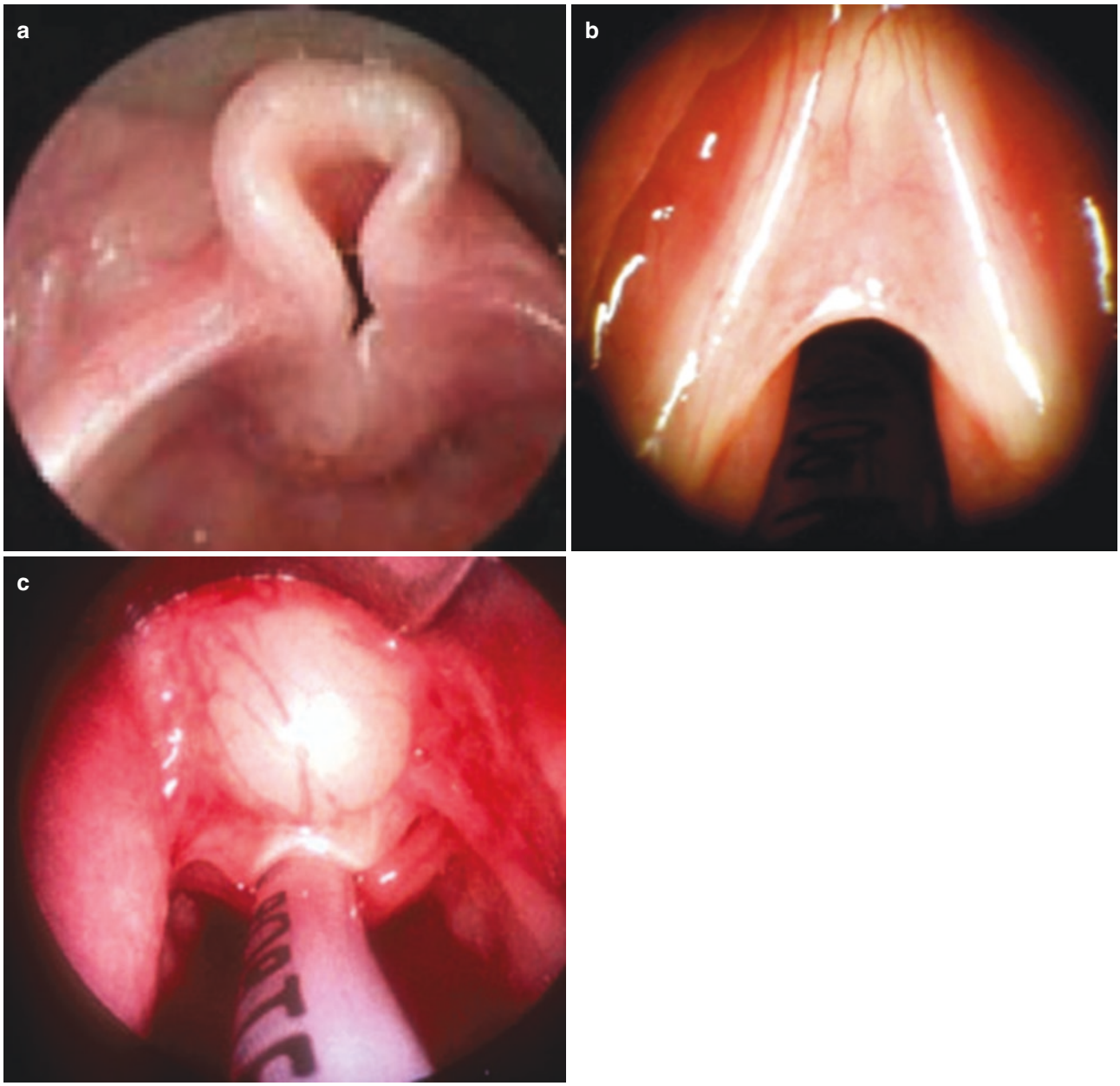

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Fig. 9.1 Congenital causes of upper airway obstruction **a** Laryngomalacia. **b** Anterior glottic web. **c** Vallecular cyst. (Photographs courtesy of pediatric otolaryngologist Aileen Wertz, MD)

stridor that begins in early infancy. Most patients have a history of stridor that is audible whenever the child is excited, agitated, or crying, beginning from the first days of life. This is commonly a self-limiting, developmental disorder in that the "floppy" larynx becomes more rigid and less obstructing with time. Endoscopically, the epiglottis is seen to fold over the larynx on inspiration. Another finding is varying degrees of prolapse of the arytenoid cartilages into the center of the larynx on inspiration. These infants may have feeding problems, and the stridor often worsens with minor respiratory tract infections. Through continuous noninvasive monitoring, it has been demonstrated that infants who have laryngomalacia are more likely than age-matched controls to have transient episodes of hypoxemia and hypercarbia, although these

episodes are usually not life-threatening. As the disorder improves over time, these infants rarely require an artificial airway or other surgical intervention.

Unilateral or bilateral *vocal cord paralysis* may occur in otherwise healthy newborns and has been associated with birth trauma. The prognosis for eventual recovery is very good for idiopathic and birth-related vocal cord injuries. However, vocal cord paralysis also may be associated with other neurological diseases and increased intracranial pressure. Restoration of abductor function has been variable with most affected patients recovering provided that the inciting event is resolved.

The prognosis for recovery of vocal cord function is good for patients with birth related paralysis.

Craniofacial dysmorphism (as in Pierre Robin and Treacher Collins syndromes) causes stridor as a result of micrognathia with posterior displacement of the tongue. *Midface hypoplasia* can contribute to upper airway obstruction in Pfeiffer, Crouzon, and Apert syndromes. *Macroglossia* (as in Beckwith-Wiedemann syndrome, congenital hypothyroidism, glycogen storage diseases, Down syndrome, and other conditions) also may cause stridor in the newborn period.

Choanal atresia presents as the neonate who makes ineffective respiratory movements with poor or absent air entry, no stridor, and deep retractions with the mouth closed yet has good air entry during inspiration when the mouth is open (e.g., during crying). Nearly half of affected neonates have other congenital anomalies (e.g., CHARGE syndrome). Unilateral choanal atresia or choanal stenosis may also occur and presents variable degrees of stridor, retractions, and poor air entry during closed mouth breathing, accompanied by resolution of symptoms with the mouth open.

Congenital laryngeal webs and *subglottic stenosis* may cause critical airway obstruction in the immediate newborn period. Some of these children may not be diagnosed correctly at presentation because endotracheal intubation in the newborn period not only provides a lifesaving airway but also temporarily bypasses the abnormality. With subsequent scarring, the child may manifest the condition again later in infancy during an upper respiratory tract infection.

Vascular rings and *slings* may cause airway obstruction in infancy. An infant who has a vascular ring may have persistent wheezing if the obstruction is in the lower trachea near the carina. Conversely, stridor is typically the major symptom when the obstruction is at a higher level of the extrathoracic trachea.

Vascular rings and slings may cause persistent wheezing if the obstruction is in the lower trachea near the carina or stridor if the obstruction is higher up in the extrathoracic trachea.

Laryngeal clefts are rare and may manifest with either stridor or symptoms of recurrent aspiration. They represent a posterior midline defect and can be difficult to visualize during flexible bronchoscopy due to the anterior angulation of the scope during laryngeal passage. Congenital *cysts* and *laryngoceles* also are uncommon causes of stridor in early infancy. As mentioned earlier, soft subglottic cysts may cause primarily expiratory sounds due to dynamic impingement on the undersurface of the glottis in expiration. These are easily visualized at flexible laryngoscopy/bronchoscopy.

Congenital *tracheal stenosis*, a rare disorder, may be limited to one or more tracheal rings but also has an extreme form in which the entire trachea may have circumferential cartilaginous rings much like lobar and segmental bronchi. It generally presents in infancy, precipitated by a respiratory infection, and may manifest with inspiratory or expiratory airflow obstruction depending on the location of the most significant narrowing. A pulmonary artery sling is present in approximately one third of patients, and less commonly cardiac anomalies are associated. Flexible bronchoscopy is very useful in delineating the extent of the stenosis, but the diagnosis may be missed without a thorough bronchoscopic exam, beyond a cursory look limited to the larynx and subglottis in the stridulous infant.

Pulmonary artery sling is an associated anomaly in patients with congenital tracheal stenosis.

Hemangiomas may develop at any level of the airway in infancy, and these may be associated with cutaneous hemangiomas. In the author's experience, these lesions are easily discernable with flexible bronchoscopy, undertaken with

sedation and topical anesthetic, with little risk of precipitating bleeding even when advancing the scope beyond the first lesion in order to examine for additional lesions. Corticosteroids (systemic or intralesional) may promote shrinkage. Prednisone and methylprednisolone may confer particular advantage due to a receptor-mediated antiangiogenic action. Interferon alpha, an inhibitor of angiogenesis, may be utilized with hemangiomas which do not demonstrate a response to corticosteroids. These hemangiomas generally regress spontaneously in the years following infancy.

9.3.2 Acquired Infectious Causes of Airway Obstruction

The most common cause of acute infectious airway obstruction is viral *laryngotracheobronchitis* (croup). The typical child is between 3 months and 4 years of age, has had a preceding upper respiratory tract infection, and has a barking cough and loud inspiratory stridor. Parainfluenza type 1 is the most common etiologic agent. Adenovirus, respiratory syncytial virus, and influenza are also causative. Pathogenically, there is edema of the subglottic airway with pale discharge. An important immunogenetic component is the demonstration of virus-specific IgE and histamine in the airways of children who develop the croup syndrome.

Bacterial tracheitis has become the most common cause of acute infectious upper airway obstruction resulting in respiratory failure.

Tracheostomy is not required for management of airway obstruction from bacterial tracheitis.

The incidence of membranous croup, also called *bacterial tracheitis*, has increased, and it has become the most common cause of acute infectious upper airway obstruction culminating in respiratory failure and requiring referral to a tertiary care pediatric intensive care unit. The prevailing belief is that this condition represents a bacterial superinfection of viral croup. The most common offending agents are *Staphylococcus aureus* and *Moraxella catarrhalis*, although *Streptococcus* and *Haemophilus* organisms have been implicated. The child usually has an initial croup-like illness that progresses in severity, with rising fever and increasing toxicity, culminating in respiratory failure, with thick purulent secretions noted upon intubation. This disorder usually is visually diagnosed at the time of laryngoscopy during intubation. Contrary to initial reports, tracheostomy generally is not necessary for treatment, and mortality should be very uncommon in children who have not suffered cardiac arrest before admission to an appropriate intensive care setting. Bacterial tracheitis has been reported as a feature of toxic shock syndrome caused by *S. aureus* and scarlet fever caused by group A *Streptococcus*.

Acute spasmodic croup manifests with recurrent nighttime onset of inspiratory stridor and croupy cough. Patients generally are afebrile, and episodes are short-lived. Recurrent episodes of croup may be misdiagnosed as spasmodic croup and instead may be manifestations of an underlying airway abnormality such as subglottic stenosis (SGS) or gastroesophageal reflux-related airway inflammation.

Retropharyngeal abscess (RPA, ◘ Fig. 9.2) is a relatively rare infectious cause of stridor in children. It usually occurs in children under the age of 5 years, characterized by high fever and difficulty swallowing, with airway obstruction to a far lesser degree than initially believed. Two large retrospective reviews reported the incidence of UAO in children with RPA as less than 5%. Computed tomography demonstrating a contrast-enhancing abscess is often diagnostic. Not all cases require surgical drainage.

Lemierre disease is a rare syndrome wherein infection from the oropharynx causes septic thrombophlebitis of the internal jugular vein and metastatic abscesses in the lung. It is caused by the anaerobe *Fusobacterium necrophorum*

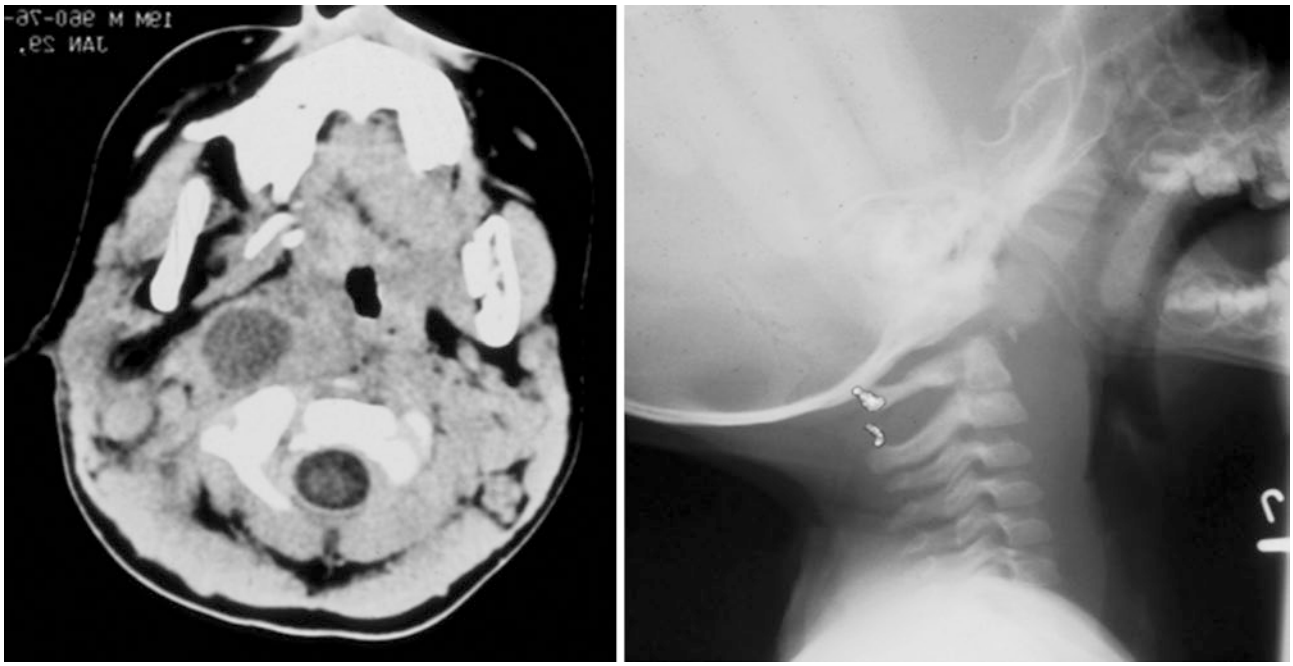

Fig. 9.2 Diagnostic imaging of a patient with retropharyngeal abscess: CT image demonstrating hypodense retropharyngeal abscess. Lateral plain radiograph demonstrating thickening of the prevertebral space

and afflicts teens and young adults with upper airway obstruction and signs of sepsis.

Acute epiglottitis (Fig. 9.3) is most commonly due to infection with *Haemophilus influenzae* type b. This disease has been seen less frequently in the past 20 years, as the result of the development of an effective vaccine. It may occur at any age, including in adulthood. Stridor, fever, and rapidly progressive respiratory distress are hallmarks of the infection. Immunocompromised hosts may develop epiglottitis from atypical organisms including *Pseudomonas aeruginosa* and *Candida* species. Noninfectious causes include trauma from instrumentation, thermal injury, and caustic ingestion.

Acute infectious mononucleosis may cause significant upper airway obstruction as a result of tonsillar hypertrophy. This condition rarely leads to respiratory failure, and the airway obstruction generally responds promptly to a short course of corticosteroids. The level of the obstruction is amenable to placement of nasopharyngeal airway with significant alleviation of airflow obstruction.

Airway obstruction from acute infectious mononucleosis rarely leads to respiratory failure and is amenable to relief with nasopharyngeal airway placement and a short course of corticosteroids.

Laryngeal papillomatosis may cause persistent stridor in children and adults at any age. Multiple, recurrent, rough-surfaced laryngeal tumors are caused by infection with the human papillomavirus (HPV). Repeated surgical excision generally is required to maintain a patent airway. Most recently, immunological therapy with interferon alpha and local treatment with the antiviral cidofovir has demonstrated beneficial effects on these tumors. The use of photodynamic therapy has shown promise but not yet demonstrated superiority in randomized trials. Likewise, case reports and small series suggest benefit from multivalent human papillomavirus vaccination. The condition tends to improve with time, presumably as the child develops immunity to the virus.

Diphtheria, caused by the gram-positive bacillus *Corynebacterium diphtheriae*, is an extremely rare infection in the United States, but it still may occur in unimmunized children.

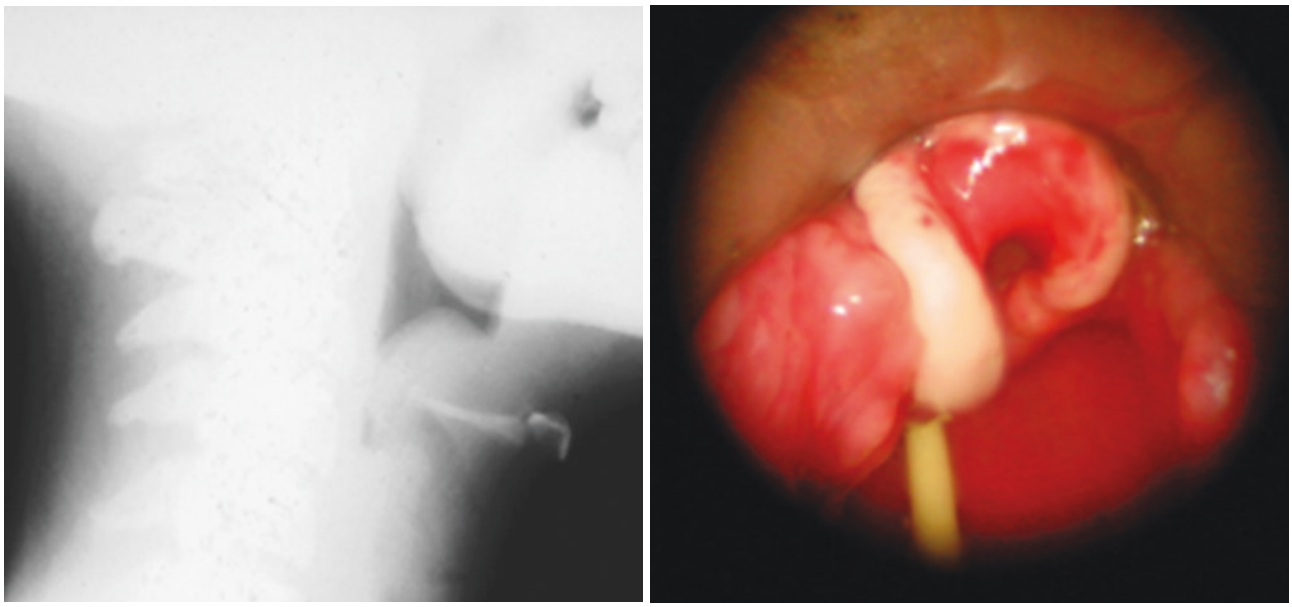

Fig. 9.3 Epiglottitis: Lateral plain radiograph demonstrating the shadow of a swollen epiglottis and direct laryngoscopy demonstrating inflamed and swollen supraglottic structures

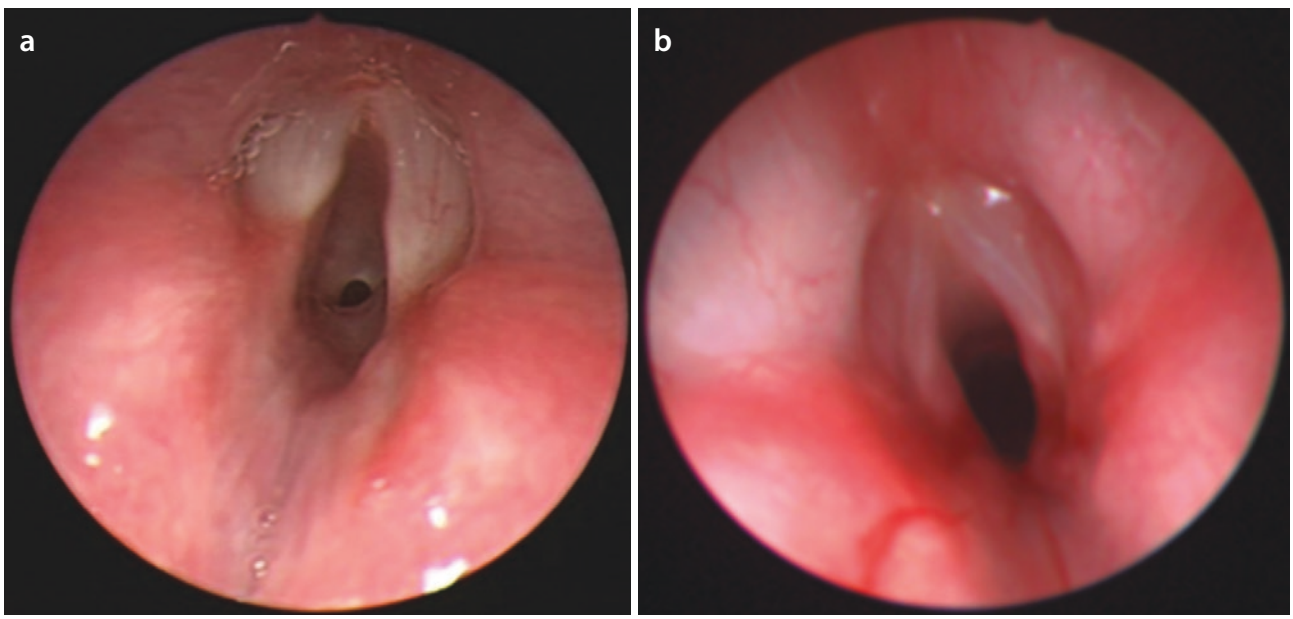

Fig. 9.4 **a** Acquired subglottic stenosis after prolonged intubation. **b** Bilateral fixed vocal folds due to posterior glottic stenosis and arytenoid scarring following prolonged intubation. (Photographs courtesy of pediatric otolaryngologist Aileen Wertz, MD)

9.3.3 Other Acquired Causes of Airway Obstruction

The pediatric intensivist must appreciate the risk of acquired subglottic stenosis (Fig. 9.4) due to endotracheal intubation. The narrowest and most susceptible area of the subglottic region is just below the vocal cords and is circumscribed by the cricoid cartilage. If this area is injured during intubation, clinical presentation of SGS can be variable in the timing and severity of UAO. Acute edema and inflammation may cause the child to become symp-

tomatic shortly after extubation. Alternatively, slow accumulation of granulation tissue in the injured subglottic region may delay symptoms for weeks following extubation.

Multiple factors contribute to the development of SGS and include the duration of intubation, traumatic intubation, reintubation, presence of an infection while intubated, undersedation, and concomitant gastroesophageal reflux. Although counterintuitive, it appears, most neonates tolerate longer periods of intubation without subglottic injury than do older children. Unlike congenital SGS, acquired SGS typically does not improve over time, and a tracheotomy may be required in severe cases. Tracheostomy often is unable to be reversed without definitive airway reconstruction. Tracheostomy carries a risk for all children, and definitive repair should be considered if possible. Tracheostomy dependence is associated with a 1–2% risk of tracheotomy-related death each year.

CNS-induced airway obstruction is complex and often multifactorial. *Bulbar dysfunction* refers to abnormalities of the control and strength of the laryngeal and pharyngeal muscles increasing resistance to airflow. Children who have suffered brain injuries may have upper airway obstruction secondary to poor supraglottic motor control and hypotonia. The tongue may obstruct the airway, or the pharynx may collapse on inspiration. This can occur as the result of long-standing severe psychomotor retardation or may be acquired as a result of hypoxic, infectious, or traumatic brain injury. It is also seen less commonly in pediatrics as a result of neuromuscular disease. *Laryngeal dystonia* is a less common condition involving the tonic adduction of the vocal cords with diminished inspiratory abduction seen in patients with hypertonicity secondary to acute (hypoxic-ischemic) or long-standing (cerebral palsy) CNS insults. *Vocal cord paralysis* with paradoxical inspiratory adduction may occur as a consequence of a variety of serious intracranial injuries. Typical patients have required a tracheostomy, although vocal cord function may improve over ensuing months, allowing decannulation.

Brain injured children may have upper airway obstruction secondary to poor supraglottic motor control and hypotonia.

Chronic upper airway obstruction with hypercarbia and apnea may occur in otherwise healthy children with *trisomy 21* or morbid obesity. The consequences of long-term indolent hypercarbia include pulmonary hypertension and congestive heart failure.

Foreign body aspiration may manifest with airway obstruction at almost any level of the pediatric airway. Stridor may be one of the presenting symptoms when a foreign body lodged in the upper esophagus has caused progressive airway obstruction secondary to localized edema that develops over days to weeks. Foreign bodies lodged in the upper airway itself often cause sudden death. Foreign bodies aspirated into the lower airway generally manifest with a combination of wheezing, cough, and infection. Clinical suspicion can be confirmed by appropriate roentgenographic studies. The definitive therapy is removal of the foreign body using rigid bronchoscopy techniques in an operating room, thereby permitting tracheostomy or thoracotomy if either of these becomes necessary.

Corticosteroid therapy is not beneficial for an inhalational or caustic injury to the airway.

Thermal or *chemical trauma* of the airway may cause swelling and upper airway obstruction significant enough to precipitate acute respiratory failure. Flash burns of the face from injudicious use of volatile liquids to start fires commonly cause oropharyngeal and laryngeal edema that may seriously compromise the airway. Ingestion of corrosive substances likewise may cause burns of the oropharynx and larynx that produce acute obstructing edema that requires placement of an artificial airway. Empirical use of parenteral corticosteroids is not beneficial for an inhalational or caustic injury. In the case of flash burn injuries to the face, early intubation prior to the development of maximal oropharyngeal swelling may be lifesaving.

External trauma to the head and neck may cause upper airway obstruction by dislocating the laryngeal cartilages or by causing a hematoma or edema. This type of injury is rare in the spectrum of pediatric traumatic injury.

In the oncology population, *severe mucositis* secondary to chemotherapy can on rare occasions lead to upper airway obstruction with pseudomembranes.

Upper airway swelling can develop suddenly after ingestion of an allergen, an insect sting, or an environmental exposure. This may occur with highly allergic individuals *(anaphylaxis)* or with hereditary *angioneurotic edema*, an extremely rare condition. The treatment goal for these children is rapidly securing an airway, in which case the prognosis is good.

9.4 Assessment

9.4.1 Examination

Airflow becomes more turbulent, and the pressure gradient necessary to support flow increases when flow rate increases as during excitement and crying.

The clinician first should assess the child's level of distress in a manner that contributes least to the child's fear and anxiety. Airflow becomes more turbulent, and the pressure gradient necessary to support flow increases when flow rate increases as during agitation and crying. Thus, the clinician should attempt to obtain as complete an assessment as possible in the least threatening manner because agitation and crying worsen the relative degree of airway obstruction and the attendant work of breathing. For the child who remains alert and aware, a useful approach is to obtain a brief history from the parents or transporting personnel while merely observing the child from a nonthreatening distance. After noting all physical signs that do not require direct physical contact with the patient, the examiner should gently approach the child to auscultate the chest and assess the circulation.

The child's appearance gives important clues to the degree of respiratory compromise. The degree of the child's anxiety can be an important clue to the severity of the airway obstruction. Many children who have croup appear quite calm and content sitting in their parent's arms when not being "threatened" by an examiner. Although these children may have significant stridor, their level of comfort indicates that they are not significantly hypoxic or hypercarbic. Conversely, a child who remains persistently anxious or who has become somnolent to the point of no longer interacting with those around him may be significantly hypoxic or hypercarbic.

Stridor needs to be assessed in the context of the quality of inspiratory breath sounds. Diminished stridor may indicate severe restriction of airflow.

Use of accessory muscles indicates the degree of inspiratory effort. Stridor needs to be assessed in the context of the inspiratory breath sounds. Generally, stridor becomes louder as airway obstruction worsens. However, in extreme cases, stridor may become barely audible as inspiratory flow almost ceases. It is the quality of the inspiratory breath sounds that differentiates improvement (breath sounds clearly heard) from rapid deterioration (breath sounds barely audible) as the reason for diminishing stridor. Respiratory rate has been reasonably well correlated with hypoxemia, but little correlation has been established with hypercapnia. The degree of hypoxemia is easily assessed by pulse oximetry monitoring, which most children tolerate well. In the differential diagnosis of acute infectious upper airway obstruction, the presence of fever, drooling, cough, a forward-leaning posture, or the appearance of toxicity is useful in leading toward a specific diagnosis and approach to therapy.

A variety of scoring systems have been proposed to aid in assessing the degree of upper airway obstruction. Such systems help focus observation and provide a guide to the effects of therapy. However, the usefulness of scoring

systems is limited because the symptoms of airway obstruction are highly dependent on the level of arousal which will vary with hypoxia and hypercarbia but also with wakefulness, hunger, fearfulness of strangers, and other variables not directly related to the level of airway obstruction. Rather, it is observation of the typical waxing and waning course over time and in response to therapies which is key to assessment.

The usefulness of scoring systems is limited because the symptoms of airway obstruction are highly dependent on the level of arousal which is affected by circumstances not directly related to the level of airway obstruction.

The quality of the inspiratory stridor can help to identify the level of obstruction. Supraglottic obstruction commonly results in a sonorous, low-pitched stridor (stertor) with muffled voice, whereas laryngeal obstruction (particularly abductor vocal cord paralysis) is most commonly characterized by high-pitched stridor and weak voice or cry. Finally, with subglottic obstruction, the stridor is loud, moderately high pitched, and the voice hoarse.

9.4.2 Diagnostic Evaluation

Clinical findings in bacterial tracheitis seem to evolve over time from those of more typical croup to those suggestive of epiglottitis

With acute, infectious upper airway destruction, diagnostic assessment and initial treatment should occur in a rapid and orderly manner. Depending on the cause, the child's condition may deteriorate quickly. Diagnosis is relatively straightforward when a young child has the classic symptoms of viral croup: upper respiratory tract infection prodrome with subsequent development of stridor, a barking cough, and a mildly elevated temperature. Likewise, an older child who has the classic presenting features of epiglottitis (acute onset of a sore throat, a high fever, a muffled voice, unwillingness to swallow, a toxic, distressed appearance, and rapidly progressive respiratory distress) is also readily diagnosed. In practice, however, many children have varying combinations of these features. Indeed, the emergence of membranous laryngotracheobronchitis (bacterial tracheitis) has complicated the diagnosis because this disorder's clinical findings seem to evolve over time from those of more typical croup to those suggestive of epiglottitis.

Controversy still exists over whether roentgenographic neck examinations should be done in a moderately ill child of any age who has acute upper airway obstruction. The need to rapidly differentiate croup from epiglottitis has markedly diminished since the success of *Haemophilus influenzae* type b vaccination. Roentgenographic confirmation of the diagnosis of croup is often unnecessary. In an uncooperative child who has classic croup, it is not uncommon for a lateral neck roentgenogram to be of such poor quality (usually an oblique view) that a misinterpretation of epiglottis is not uncommon. This usually results in an unnecessarily high level of anxiety and referral to a tertiary care pediatric center. The more important scenario, which has now become rare, is that of the child with epiglottitis who develops acute upper airway obstruction and respiratory arrest while being positioned for roentgenographic evaluation, necessitating emergency resuscitation in a suboptimal environment.

Finally, membranous laryngotracheobronchitis has no specific roentgenographic features. Because of these considerations, many pediatric institutions forgo routine roentgenographic evaluation of the upper airway for the child with significant distress if bacterial infection (epiglottitis, retropharyngeal abscess, and membranous laryngotracheobronchitis) is suspected. Rather, the airway is visualized in the operating room by a pediatric anesthesiologist with surgical backup and provisions for emergency tracheostomy if necessary. This approach affords maximal safety for children who have the most dangerous

disease, mainly epiglottitis; it also affords an opportunity for early diagnosis and intervention in cases of membranous laryngotracheobronchitis.

Flexible laryngoscopy and bronchoscopy allow direct diagnostic evaluation and videotaping of airway dynamics for patients with subacute or chronic stridor and can be performed safely at the bedside.

In the case of a neonate or child who has subacute or chronic stridor and no significant respiratory embarrassment, several diagnostic approaches can be taken. A barium swallow or fluoroscopic evaluation of the airway can be helpful in demonstrating congenital lesions. Flexible laryngoscopy and bronchoscopy also allow direct diagnostic evaluation and recording of airway dynamics. With experienced personnel and appropriate monitoring, this procedure can be done safely at the bedside.

Blood sampling is a low priority in a child who has acute infectious upper airway obstruction. Noninvasive pulse oximetry is a more appropriate way to monitor hypoxemia.

Blood sampling is a low priority in a child who has acute infectious upper airway obstruction because the crying and struggling elicited by this painful procedure increase both the metabolic rate and the inspiratory work of breathing through the obstructed airway. Children who have croup or epiglottitis may have mild hypoxemia in room air, which may be due to atelectasis or early secondary pneumonia. Noninvasive pulse oximetry is a more appropriate way to monitor hypoxemia than intermittent sampling of blood gases. Progressive hypoxemia in supplemental oxygen is a serious warning sign. Blood gas monitoring may be useful in cases of more subacute exacerbations of chronic upper airway obstruction as in the neurologically impaired child or the child with chronic upper airway obstruction with trisomy 21 or morbid obesity. In such cases, blood gas analysis can reveal useful information concerning the relationship of the current episode to baseline function (e.g., acute on chronic respiratory acidosis) and has implications regarding the urgency of intervention.

If an artificial airway is required, cultures of blood, purulent tracheal secretions, or the surface of the epiglottis can be obtained.

9.5 Management

9.5.1 Triage and Initial Stabilization

A child who has significant airway obstruction from any cause, as well as any child suspected of having foreign body aspiration or an acute airway injury, should be hospitalized immediately. These children should be placed in a pediatric intensive care unit or in a continuously monitored area in an institution that contains a pediatric intensive care unit to which the child can be transferred immediately should deterioration occur. A child who has mild croup and does not have stridor during quiet breathing need not be hospitalized. A child who has croup and has stridor at rest but who responds well to specific therapies does not necessarily require transfer to a pediatric tertiary care center.

Children suspected of having epiglottitis should not be transported to another facility prior to endotracheal intubation.

A child who has significant airway obstruction should be transported by ambulance (air or ground, depending upon the distance and geography) and receive oxygen continuously. The child must be accompanied at all times during transport by personnel skilled in airway management. Children suspected of having epiglottitis should not be transported before endotracheal intubation because of the risk, well documented in the medical literature, of cardiorespiratory arrest during transport when the airway has not been secured beforehand. It is a rare circumstance when a community hospital cannot assemble a team for controlled endoscopic examination and nasotracheal intubation in the operating room before transport.

Any child with signs of progressive airway obstruction should have cardiopulmonary and pulse oximetry monitoring and receive humidified oxygen in an intensive or intermediate care unit that has a central alarm station or transmission of alarm parameters to nursing staff. The theory of withhold-

ing oxygen so that desaturation can be used to detect early hypoventilation is not recommended since the child may have mild hypoxemia due to ventilation perfusion mismatching independent of hypoventilation. Additionally, hypercapnia is likely quite variable in these patients, and it is of little physiologic consequence, and thus risking hypoxemia in order to detect it is unwise.

The alert child should be allowed to maintain the position that is most comfortable. Most children who have an obstructed airway prefer to sit up if they are developmentally capable of doing so, and the position of most comfort (and therefore least airway obstruction) may be on the lap of a caregiver. For the somnolent or neurologically impaired child with upper airway obstruction due to abnormalities of dynamic control of the supraglottic or pharyngeal airway, the lateral recumbent position with neck extension may afford some relief of airway obstruction.

For the somnolent or neurologically impaired child with upper airway obstruction, the lateral recumbent position with neck extension may afford some relief of airway obstruction.

Nasopharyngeal airways can provide both relief of obstruction and a conduit for nasopharyngeal and nasotracheal suctioning. These are most useful with obstruction at a level above the laryngeal cartilages, such as when due to the tongue, tonsils, or pharyngeal walls. The length of the nasopharyngeal airway insertion should be equal to the distance from the nostril to the tragus and can be confirmed clinically with auscultation. While soft rubber catheters are minimally traumatic, on occasion they are not firm enough to avoid compressive obstruction by adjacent soft tissues. A trimmed uncuffed endotracheal tube may also be used as a nasopharyngeal airway in such circumstances. Oropharyngeal airways are rarely useful for any longer than brief resuscitative efforts due to the difficulty with long-term stabilization and tendency to induce gagging in all but the most neurologically depressed patients.

The length of the nasopharyngeal airway insertion should be equal to the distance from the nostril to the tragus and can be confirmed clinically with auscultation.

The effectiveness of nebulized epinephrine in the management of acute laryngotracheobronchitis is well established. Its vasoconstrictor properties at the site of inflamed swollen mucosa make it useful for the treatment of any inflammatory lesion of the airway including post-extubation upper airway swelling. Aerosolized racemic epinephrine (2.25%, 0.5 ml in 2.5 ml of saline) or L-epinephrine (1%, 0.5 ml in 2.5 ml of saline) in oxygen via face mask provides prompt temporary improvement in airflow. The dose is prescribed as a fixed volume and ratio of drug to saline, since the child's minute ventilation will proportion the dose received to his/her size. The most recent multi-study review shows no difference in efficacy between the two forms of nebulized epinephrine and no advantage of administration by IPPB (intermittent positive pressure breathing) over simple nebulization. The most significant toxicity of aerosolized epinephrine in a healthy child is tachycardia, which is well tolerated. At times, the heart rate declines after administration of epinephrine aerosol, coincident with the improvement in airflow and reduction of dyspnea. Aerosol treatments may be repeated every 15–30 min, as necessary, for palliation of upper airway obstruction.

The effectiveness of aerosolized epinephrine has been demonstrated for treatment of upper airway obstruction due to acute laryngotracheobronchitis, post-extubation airway edema, angioedema, and anaphylaxis.

It should be noted that a response to aerosolized epinephrine may not be long-lasting as the duration of action is only up to 2 h, at which point the child may "rebound" back to the previous state and require further therapy. Children who require repeated dosing should be hospitalized in a monitored intensive or intermediate care unit.

9.5.2 Definitive Therapy

The definitive therapies for the three most common causes of upper airway obstruction—viral croup, epiglottitis, and membranous laryngotracheobronchitis (bacterial tracheitis)—are each distinct. Most patients who have croup

respond to supportive medical treatment, which includes humidified oxygen, inhalation of epinephrine aerosol, and systemic corticosteroids. It is the unusual patient who has laryngotracheobronchitis to require an artificial airway. A diminishing response to epinephrine or the development of hyperpyrexia and toxicity may be evidence of bacterial superinfection, heralding the onset of membranous laryngotracheobronchitis (bacterial tracheitis).

Corticosteroids have been demonstrated to be effective for treatment of upper airway obstruction of multiple etiologies.

Corticosteroids have become an accepted component of therapy for inflammation-related upper airway obstruction. Inhaled budesonide has been shown to be equally effective as parenteral or enteral dexamethasone in the treatment of upper airway obstruction due to acute laryngotracheobronchitis. A meta-analysis of multiple studies has demonstrated the effectiveness of systemic corticosteroids in the treatment of post-extubation upper airway obstruction and prevention of the need for reintubation. Corticosteroids are also effective for upper airway obstruction due to infectious mononucleosis and hemangioma.

Helium-oxygen gas mixtures lower the density of inspired gas significantly, reduce airway resistance during turbulent airflow, and may temporarily relieve and palliate airflow obstruction.

Helium can be used to replace nitrogen as the carrier gas for oxygen (heliox) to reduce the work of breathing in patients who have critical narrowing of the upper or lower airway. Helium concentrations of 60% or greater (i.e., oxygen concentration of 40% or lower) will effectively lower the density of inspired gas and reduce airway resistance during turbulent airflow. Recent multi-study review has demonstrated the efficacy of helium-oxygen gas mixtures in the treatment of croup. Although helium-oxygen gas mixtures may temporarily relieve and palliate airflow obstruction, it is not definitive therapy in itself and cannot be used effectively in children requiring oxygen concentrations above 40%. Heliox should not be used in cases of acute epiglottitis.

9.5.3 Mechanical Support of the Upper Airway

The distensibility of the upper airway structures can be taken advantage of in the palliation of some forms of obstruction. Recall that the extrathoracic airway is narrowest during inspiration due to the collapsing effect of relatively negative intraluminal pressure. Continuous positive airway pressure (CPAP) can be used to distend the supraglottic airway and relieve obstruction. Nasal prongs or mask can be used to deliver CPAP.

The use of high-flow humidified oxygen via nasal cannula has gained popularity as a means to comfortably deliver distending pressure to the airways. The development of reliable humidification systems for high-flow gas delivery has overcome the damaging drying effects of high gas flows when delivered to the nares or trachea. Such systems deliver high flows of variable oxygen concentrations (up to 100%) to the proximal airway and provide an unquantifiable distending pressure which can be more comfortable than conventional CPAP delivery systems. High-flow humidified oxygen also decreases dead space ventilation and resistance forces which ultimately reduces the work of breathing. The added comfort makes the use more easily applied to pediatric patients than CPAP.

Optimal treatment in all cases of acute epiglottitis is securing the child's airway, preferably by endotracheal intubation. Tracheostomy for treatment of acute epiglottitis is unusual. Inspection and intubation are carried out in the operating room, with the patient undergoing general anesthesia and a pediatric anesthesiologist managing the airway. A surgeon must be present to perform either rigid bronchoscopy or tracheostomy if intubation is not possible.

Intubation for epiglottitis generally lasts 18–36 h, until parenteral antibiotics effective against *H. influenzae* have controlled the infection. A second- or third-generation cephalosporin generally is used because of the prevalence of ampicillin-resistant strains. Repeated visualization of the epiglottitis is not necessary for determining the timing of elective extubation, as success with empiric extubation is nearly 100%.

Many cases of bacterial tracheitis require endotracheal intubation to secure an adequate airway. Consequently, most diagnoses are made at the time of intubation. More recent case reports suggest that early diagnosis and initiation of appropriate antimicrobial therapy can ameliorate the course of milder cases, preventing progression to respiratory failure. The most common infectious agents that cause bacterial tracheitis are *S. aureus*, *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, and *S. pyogenes*. Empiric antibiotic coverage should consist of antistaphylococcal coverage (with consideration of vancomycin for possible methicillin-resistant isolates) paired with a second- or third-generation cephalosporin active against *Moraxella* and *Haemophilus* organisms. Antimicrobial coverage should be narrowed after identification of the causative organism. Generally, extubation is attempted only after thick, purulent secretions have diminished markedly and an air leak is heard on inspiration around the endotracheal tube. The requirement for an air leak is arbitrary because some children have a successful trial of extubation after intubation even without an air leak. The relationship of the patient's endotracheal tube diameter to the usual size for age is an additional consideration.

For the child intubated secondary to airway obstruction from bacterial tracheitis, extubation is attempted only after thick, purulent secretions have diminished markedly. The presence of an air leak around the endotracheal tube is encouraging but may not preclude a trial of extubation.

Another scenario encountered in the emergency department involves a child with long-standing, mild upper airway obstruction who has a sudden exacerbation of obstruction. This may be an infant with mild to moderate laryngomalacia who has increasing difficulty with oropharyngeal secretions arising secondary to a viral infection. Or it may be a child with poor supraglottic muscle tone as a result of severe psychomotor retardation who has an increase in upper airway obstruction due to increased volume of secretions or further decrease in mental status secondary to seizures or the effects of antiepileptic medications. Noninvasive methods of supporting upper airway patency with positive pressure or minimizing turbulence with helium-oxygen mixtures can be effective and obviate the need for airway instrumentation. These children may have chronic hypercapnia of varying degrees and generally will not precipitously lose their airways, and their treatment may be guided by judicious sampling of blood gas parameters to avoid extreme hypercapnia and acidosis.

The application of positive airway pressure to distend the supraglottic airway may be successful in the child with long-standing, mild upper airway obstruction who has a sudden exacerbation of obstruction.

Most children who have tracheobronchial foreign bodies are not in respiratory distress on arrival because the foreign bodies usually are not located in the proximal airway. In the very rare instance in which the patient is moribund, back blows, chest thrusts, or Heimlich abdominal thrusts may be performed (as appropriate for age) if foreign body aspiration is deemed likely. If these procedures are unsuccessful, direct examination of the airway with a laryngoscope is warranted. If a foreign body is seen to be wedged in the larynx or subglottic space, an emergency cricothyroidotomy may be necessary. If no foreign body is seen, endotracheal intubation should be performed because a foreign body may have migrated to the distal trachea. The only recourse in such circumstances is to push the foreign body forcibly into the right mainstem bronchus and ventilate the left lung. This situation is exceedingly rare.

The clinician is guided in responding to the needs of all these children by remembering the "ABCs" of basic life support—*airway, breathing*, and *circulation.* Initial assessment of the child's upper airway function focuses on the degree

of airway obstruction and the efficiency of ventilation. The clinician must determine whether the airway is *stable* and patent (which requires no intervention) or *maintainable* (the airway is compromised but can be maintained with basic interventions of oxygen, suctioning, and positioning). The third possibility is that the airway is judged to be *unstable*—this requires immediate placement of an artificial airway to maintain patency. Nasopharyngeal and endotracheal airways are the airway adjuncts of choice to maintain patency of an unstable airway.

The clinician must determine whether the airway is stable and patent, maintainable, or unstable which requires immediate placement of an artificial airway to maintain patency

9.6 The Difficult Airway

The intensivist, being the clinician charged with caring for the most compromised patients, will inevitably be confronted at some time with the child requiring intubation who possesses an anatomically challenging airway. Even the normal infant and small child present a challenge to airway management due to the relatively larger tongue and more anterior and cephalad placement of the larynx relative to the adult. It is imperative that a plan of action is in place that describes the approach to the child with an unanticipated difficult airway.

Nasopharyngeal and endotracheal airways are the airway adjuncts of choice to maintain patency of an unstable airway.

Effective airway management begins with assessing the child for the potential of a difficult airway. Several anatomic features are predictive of a difficult airway (Table 9.1) and include congenital, developmental, or acquired anomalies of the airway. Goldenhar syndrome, Pierre Robin sequence, Pfeiffer syndrome, Crouzon syndrome, Apert syndrome, Treacher-Collins syndrome, Klippel-Feil syndrome, arthrogryposis multiplex, and the mucopolysaccharidoses are often associated with difficult airways. Micrognathia or mandibular hypoplasia combined with relative or absolute macroglossia can make visualization of the structurally normal larynx difficult. Conversely, the progressive soft tissue infiltration with glycosaminoglycans occurring in the mucopolysaccharidoses can lead to supraglottic and glottic structures that are so thickened and distorted as to render them unrecognizable.

9.6.1 Pharmacologic Considerations

The American Society of Anesthesiologists has published updated practice guidelines for the management of the difficult airway. The initial key decision point in dealing with the difficult airway is the choice between awake intuba-

Table 9.1 Conditions associated with difficult intubation

Anatomic abnormality	Associated conditions
Small mouth (microstomia)	Freeman-Sheldon syndrome, Hallermann-Streiff syndrome
Mandibular hypoplasia (micrognathia)	Pierre Robin sequence, Treacher-Collins syndrome, Goldenhar syndrome, Apert syndrome
Large tongue (macroglossia)	Down syndrome, Beckwith-Wiedemann syndrome, mucopolysaccharidoses, anaphylaxis, trauma
Limited neck mobility	Klippel-Feil syndrome, cervical spine immobilization
Abnormal head size	Apert syndrome, Crouzon syndrome, microcephaly, macrocephaly

tion and intubation attempts after the induction of anesthesia. While attempting to intubate the awake child preserves the patient's strength and ventilatory drive, the presence of distress with struggling and unsuppressed airway reflexes substantially increases the difficulty of successful intubation. A basic tenet in approaching a potentially difficult airway is to avoid burning one's bridges by using the shortest lasting sedatives or neuromuscular blockers to facilitate intubation. None of the non-depolarizing agents is of sufficiently short duration to allow the resumption of spontaneous ventilation within minutes of unsuccessful intubation attempts. The shortest acting non-depolarizing agent (rocuronium) has a duration of action of 30–40 min. Succinylcholine has the pharmacokinetic profile to afford very brief relaxation with rapid recovery if intubation fails. However, the use of succinylcholine requires the use of a vagolytic medication in the very young. Its use may result in muscle fasciculations, occasionally resulting in transiently increased masseter tone or vomiting. Succinylcholine carries the risk of hyperkalemia in at-risk groups who not uncommonly will be the patients with difficult airways. These include children with chronic skeletal muscle disease (e.g., Becker or Duchenne muscular dystrophy) and denervating neuromuscular disease (e.g., cerebral palsy with paralysis). These concerns make succinylcholine a less than optimal choice.

An appropriate sedative agent must be given prior to the use of neuromuscular blockade. Propofol offers the advantage of rapid onset of titratable relaxation and complete suppression of airway reflexes, coupled with very short duration of action should airway attempts fail. Induction of anesthesia with incremental doses of 1–2 mg/kg up to a total of 3–5 mg/kg can afford an optimal first look at the difficult airway with the ability to return to spontaneous ventilation within 5 min. The only significant risk is for hypotension in the hemodynamically unstable child. This can be ameliorated with fluid administration prior to intubation. Alternative sedative agents include ketamine, fentanyl, and/or midazolam. Etomidate, if used, should be avoided in children with sepsis.

Multiple randomized controlled trials have demonstrated longer times to desaturation thresholds of 93–95% oxygen concentration after 3 min of preoxygenation. Recent data from the National Emergency Airway Registry for Children has demonstrated arterial oxygen desaturation to less than 80% in 19% of all PICU intubations, 23% of those children with respiratory indication for intubation. Moderate and severe desaturations (SaO_2 < 70%) were independently associated with the occurrence of adverse hemodynamic events.

The initial key decision point in dealing with the difficult airway is the choice between awake intubation and intubation attempts after the induction of anesthesia.

When uncertain of the ability to secure intubation of the airway, one should use the shortest lasting sedatives or neuromuscular blockers to facilitate intubation.

9.6.2 Ventilation Without Intubation

For the child who cannot be intubated in the conventional manner under direct laryngoscopic visualization yet requires assisted ventilation, the ASA recommends several alternate techniques and devices to provide ventilation in the absence of endotracheal intubation. The methods applicable to children at the bedside include two-person mask ventilation, oral and nasopharyngeal airways, laryngeal mask airway, retroglottic devices (King tube), and transtracheal jet ventilation.

Two-person mask ventilation can overcome high upper airway resistance in the child with severe upper airway obstruction. Oral and nasopharyngeal airways are useful in allowing BMV in the child who has failed intubation.

One can achieve short-term ventilation of the unintubatable child using oral and nasopharyngeal airways and bag-mask positive pressure ventilation.

The laryngeal mask airway (LMA) has been the most successful and widely accepted form of supraglottic artificial airway, offering some of the advantages of endotracheal intubation without the need to visualize and intubate the larynx. It has become the consensus second-line airway. The LMA consists of an

inflatable mask or bowl portion attached at the distal end of the airway tube. Rotational technique with partially inflated cuff is reported to have the highest rate of successful insertion. On insertion, the operator's index finger, placed at the junction of the airway shaft and the mask, guides the LMA along the posterior structures from the palate down the posterior pharyngeal wall into the hypopharynx to rest with the tip at the upper esophageal sphincter where it can advance no further. Inflation of the anterior-facing mask provides a low pressure seal against the glottis allowing positive pressure ventilation. Ease of insertion is the greatest advantage of the LMA. It has found widespread application in the routine use for anesthetic management of patients of all ages and has also been successfully used in the delivery room resuscitation of newborns. It can be used with reliable success by personnel not trained in endotracheal intubation. In the hands of individuals trained for either procedure, the LMA provides an airway with less potential for trauma and stress response than laryngoscopic intubation. One of the primary disadvantages of the LMA is its inability to separate the respiratory and alimentary tracts with the risk of aspiration in the event of vomiting. Finally, the LMA affords no means of suctioning the airway below the glottis. Thus, in patients with significant lung disease, the LMA can provide only temporary support through positive pressure ventilation. The LMA has found widespread use in anesthetic management of patients with normal lungs and in resuscitation of neurologically depressed neonates. Most recent systematic review demonstrated superiority of laryngeal mask airway (LMA) over bag-mask ventilation for neonatal resuscitation and the ability to rescue failed bag-mask ventilation with LMA without resorting to endotracheal intubation in this population.

The laryngeal mask airway (LMA) has been the most successful and widely accepted form of supraglottic airway.

Retroglottic devices are laryngeal tubes that allow ventilation without tube intubation through the vocal cords. When the tube is placed in the upper airway, a large pharyngeal balloon seals the oropharynx, and a smaller balloon seals the esophagus. The net effect of these seals is the direction of airflow to the glottic opening while blocking airflow into the esophagus or out the oropharynx. There are several iterations of these laryngeal devices (Combitube, King tube) that are now available in pediatric sizes.

One of the primary disadvantages of the LMA is the inability to separate the respiratory and alimentary tracts with the risk of aspiration in the event of vomiting.

Transtracheal jet ventilation uses either specialized ventilator or high-pressure-driven valve circuit via a catheter passed through the cricothyroid membrane. Required equipment includes a high-pressure oxygen supply (wall outlet), flow regulator and supply tubing, jet injector, oxygen tubing, Luer lock connector, and an intravenous catheter (14- or 16-gauge). Specialized, reinforced catheters are less likely to kink after removal of the needle. A 14- or 16-gauge catheter is introduced through the cricothyroid membrane, and air is aspirated from a syringe. The catheter is advanced into the trachea and connected to the oxygen tubing using a Luer lock connection. Gas flow is controlled using the jet injector. Adequacy of ventilation is judged by listening for breath sounds and observing chest rise. Transtracheal jet ventilation has the advantage of rapid institution of ventilation in the patient with a difficult airway if the components are previously assembled and allows ventilation during airway placement. It has the disadvantages of requiring a high-pressure gas source and depends on patency of the upper airway for ventilation. In small children, bag ventilation through 14- or 16-gauge catheter may be possible. The catheter can be connected to a 3 ml syringe which then can be connected to a 7.0 ETT tube connector. The bag (Mapleson or self-inflating) can then be connected, and ventilation can be attempted. Complications include subcutaneous emphysema, pneumomediastinum, pneumothorax, or other types of barotrauma. The use of transtracheal ventilation is limited to situations where intubation and supraglottic devices have failed (e.g., severe maxillary and or facial trauma, angioedema) (Fig. 9.5).

In patients with significant lung disease, the LMA can provide only temporary support through positive pressure ventilation. It is a tool that can be very useful in the difficult to visualize airway provided there is no obstruction at the level of the glottis or below.

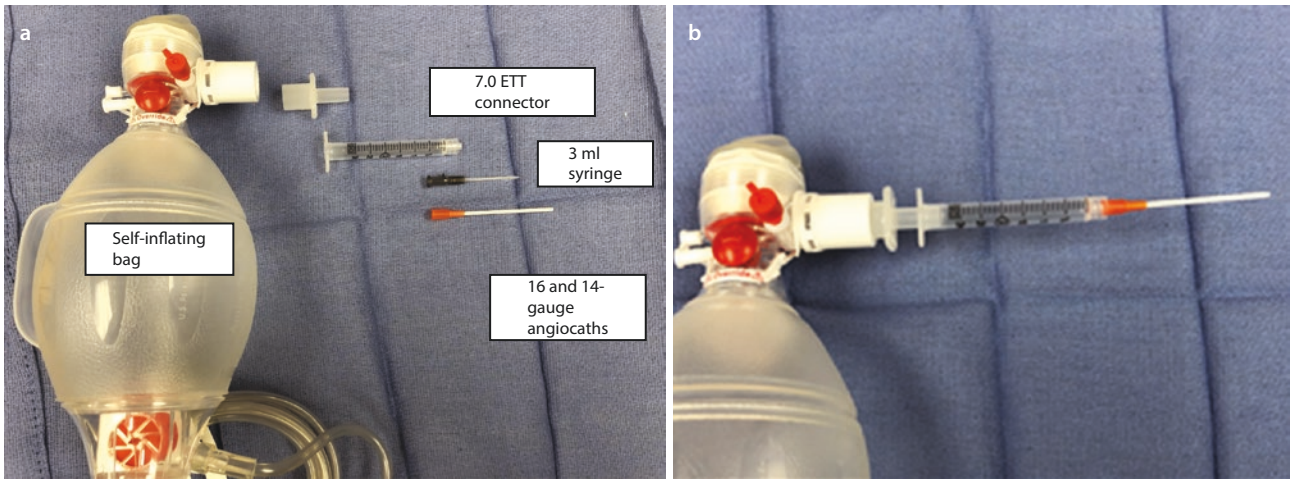

Fig. 9.5 Components of needle cricothyrotomy **a** and assembled allowing for bag ventilation **b**

9.6.3 Nonconventional Intubation Techniques

Techniques to facilitate intubation of the difficult pediatric airway following failure of conventional direct laryngoscopic visualization include fiber-optic intubation, indirect video laryngoscopes, light wand-assisted intubation, laryngeal mask airway as a conduit to intubation, retrograde intubation, and surgical or percutaneous invasive airways access. These techniques are best performed in conjunction with pediatric anesthesia and/or pediatric otolaryngology.

Passage of an endotracheal tube over a flexible fiber-optic laryngoscope is a useful technique for the difficult to visualize larynx due to extreme anterior location or supraglottic anomalies of the mandible or oral cavity. For ease of advancement of the endotracheal tube, its inner diameter must approach 1 mm greater than the outer diameter of the laryngoscope/bronchoscope. In the spontaneously breathing child, laryngoscopy with a blade is not necessary, and the endotracheal tube is placed via one of the nares to the pharynx. The scope is advanced through the endotracheal tube to the pharynx and thereafter into the trachea to the carina to assure against dislodgement. Advancement of the endotracheal tube over the scope is hindered by laryngeal reflexes and the tendency for the bevel of the tube to catch on the right vocal cord. Rotation of the tube 90° can facilitate passage. In the deeply sedated or paralyzed patient, blade laryngoscopy may be required to open the pharyngeal airway. The fiber-optic scope can be passed nasally as above or orally and the larynx intubated under direct fiber-optic visualization. Again, a 90° rotation of the endotracheal tube may be necessary to traverse the vocal cords.

Passage of an endotracheal tube over a flexible fiber-optic laryngoscope is a useful technique for the difficult to visualize larynx due to extreme anterior location or supraglottic anomalies of the mandible or oral cavity.

Video laryngoscope devices are available for intubation of the airway that cannot be visualized with line-of-sight direct laryngoscopy. Videolaryngoscopy is increasingly used as a standard intubation technique. It is also commonly used as a rescue device for the anticipated or unanticipated difficult airway. Videolaryngoscopy, if available, should be considered prior to more invasive techniques such as needle or surgical cricothyrotomy. In addition, the devices allow for real-time guidance when supervising learners.

The increasing use of videolaryngoscopy has been documented within the National Emergency Airway Registry for Children. Videolaryngoscopy has been associated with a lower incidence of tracheal intubation adverse events but not with a lower incidence of severe tracheal intubation adverse events or

with fewer attempts. However, even with adjustment for recorded patient level covariates in this retrospective analysis, it is likely that the videolaryngoscopy was used more commonly for the anticipated more difficult scenarios, and the populations were not equivalent.

Videolaryngoscopy devices include the GlideScope (Verathon Medical) and the CMAC (Karl Storz). The hyperacute angulation of the tip of the GlideScope blades precludes its use for standard direct laryngoscopy and requires training and experience to achieve proficiency. The CMAC blades are based on original blade designs used for direct laryngoscopy. Since the blades are very similar, no modification in laryngoscopy technique is required. The blades are available in traditional Macintosh and Miller sizes.

A light wand can be used as the stylet for the endotracheal tube, curved 90° toward anterior. The ability to see the transilluminated light in the anterior neck confirms location above the larynx. Blind advancement is attempted with the loss of transilluminated light indication passage into the esophagus behind the trachea. Persistence of transillumination on advancement signals successful tracheal intubation. This is essentially a blind technique with reported success rates from 65% to 90%.

The laryngeal mask airway can be used as a conduit for transglottic passage of an endotracheal tube. The smallest conventional intubating LMA is appropriate for school-age children. Small endotracheal tubes can be advanced though modified or shortened LMAs. Alternatively, a fiber-optic bronchoscope can advance through the LMA into the trachea with an endotracheal tube advanced over it. The end result of these techniques is a fairly small for age endotracheal airway.

The retrograde intubation technique utilizes a wire passed retrograde from a puncture in the cricothyroid membrane to the mouth to allow passage of an endotracheal tube into the trachea. The placement of the wire through the cricothyroid membrane should ensure passage of the endotracheal tube into the trachea. The technique does not require visualization of the larynx and may be performed rapidly by skilled practitioners. Risks attendant with the puncture of the tracheal are appreciable in the small child.

Emergency surgical airway can be accomplished via percutaneous puncture through the cricothyroid membrane with a 16–14-gauge catheter.

Emergency surgical airway can be accomplished via percutaneous puncture through the cricothyroid membrane with a 14–16-gauge catheter. Conversely, bedside tracheostomy can be accomplished in minutes when proper equipment and personnel are available. Figure 9.6 depicts an example of an algorithm for the approach to the unexpected difficult intubation.

9.7 Further Care

The focus of care in a pediatric intensive care unit revolves around vigilant provision of adequate sedation (and paralysis if necessary) to prevent additional trauma to the airway or even its inadvertent loss.

After a critically impaired airway has been diagnosed and appropriate therapy has been started, the issue of where the child will be cared for must be addressed. A child whose life depends on the patency and stability of an endotracheal tube, nasotracheal tube, or newly created tracheostomy requires the constant attention of nurses, respiratory therapists, and physicians experienced in pediatric intensive care. No amount of monitoring equipment can substitute for experienced personnel. Hence, *it is only in dire circumstances that a child with upper airway obstruction or who is intubated should be cared for in an intensive care unit that deals primarily with adults.* The focus of care in a pediatric intensive care unit revolves around vigilant provision of adequate sedation (and neuromuscular blockade if necessary) to prevent additional trauma to the airway or even its inadvertent loss. The unplanned and thus ill-timed loss of the artificial airway in a child with upper airway obstruction can be rapidly fatal and must be avoided. Airways can be kept patent by suctioning and chest

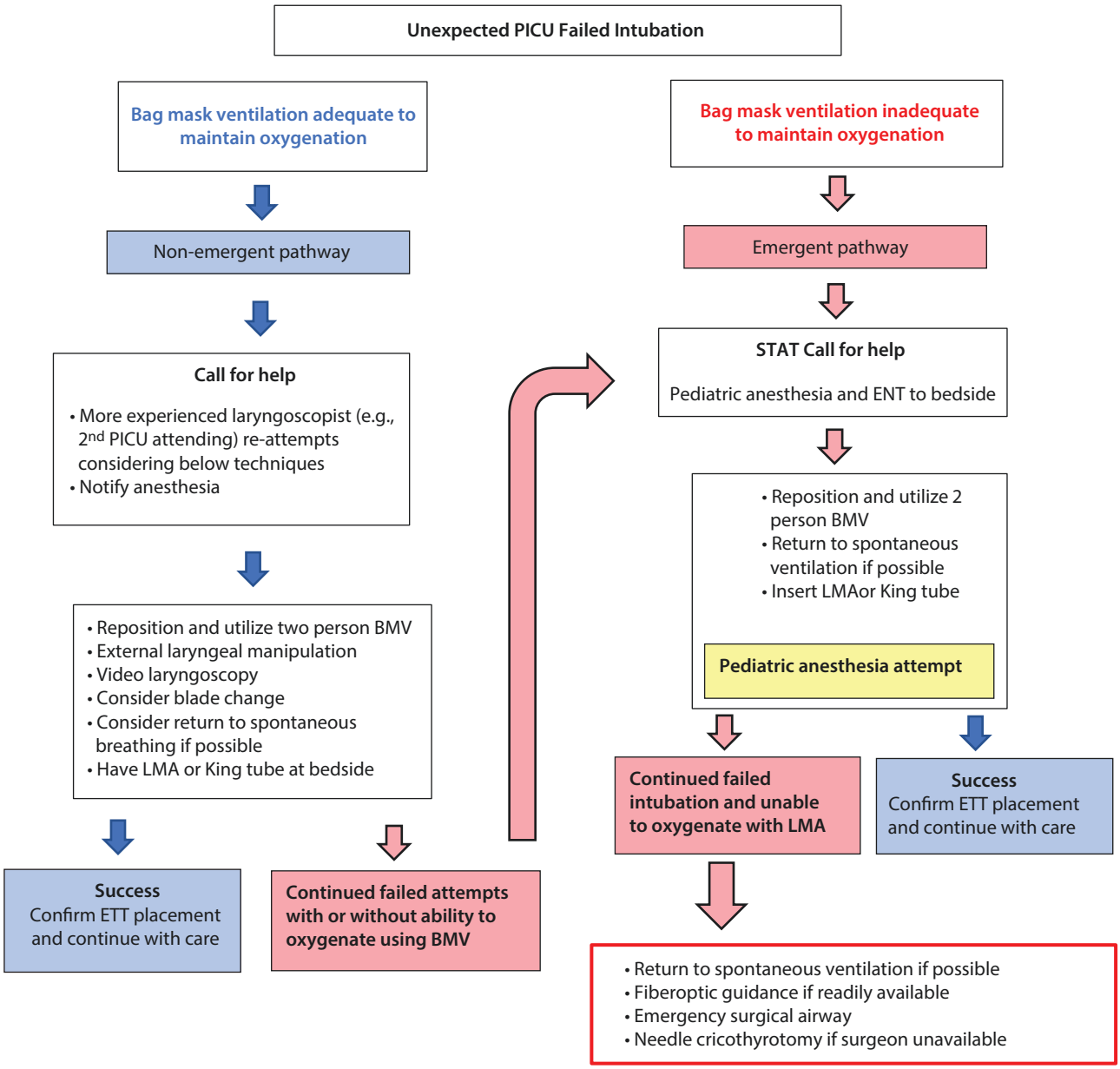

Fig. 9.6 An algorithm for the approach to the unexpected difficult intubation

physiotherapy. Providing adequate ventilation and lung expansion will prevent parenchymal complications. Attention to other organ system derangements, as well as to the routine needs of a critically ill child, also is essential. When it becomes appropriate to do so, extubation is performed only by personnel experienced in the care of the pediatric airway.

9.8 Summary

Upper airway obstruction presents a potentially life-threatening scenario to the pediatric intensivist. Characteristics of the pediatric airway including size in relation to metabolic rate, shape as relates to location of least cross-sectional area, and rigidity as relates to deformability contribute to the increased susceptibility of infants and small children to upper airway obstruction. There

are several congenital and developmental causes of upper airway obstruction which do not generally possess the danger of rapid deterioration and which afford the time for thoughtful and thorough diagnostic evaluation. The infectious causes of acquired upper airway obstruction present a much more urgent situation that must be approached with caution due to the inherently unstable nature of the infected and inflamed airway. These conditions must be addressed in an expeditious manner due to the unpredictable rate of progression of the diseases. Finally, there is a population of children with chronic compromise of upper airway function, who are prone to episodic exacerbations and whose approach to therapy can often be more measured requiring the discrimination of acute from chronic physiologic findings.

Review Questions

1. *Which of the following statements regarding bacterial tracheitis is true?*
   - A. Bacterial tracheitis commonly represents a primary invasive bacterial infection of tracheal soft tissue.
   - B. Bacterial superinfection of viral laryngotracheobronchitis is the most common cause of infectious upper airway obstruction requiring an artificial airway.
   - C. Antimicrobial agents are not effective in the treatment of bacterial tracheitis.
   - D. The most common offending agents are anaerobic bacteria of the oropharynx.
   - E. Tracheostomy is the preferred airway for small children with bacterial tracheitis because of difficulties with thick tracheal secretions.

2. *A 15-month-old male presents with acute laryngotracheitis. Upon arrival to the PICU, he has audible stridor, increased work of breathing, and a pulse oximeter reading of 88% on a simple face mask. In considering the use of heliox in this child, which of the following is true?*
   - A. The use of heliox would require monitoring of arterial blood gases because of the associated lower FiO2.
   - B. A supervised trial of heliox in the PICU may improve both ventilation and oxygenation.
   - C. A supervised trial of heliox in the PICU may improve ventilation but is unlikely to improve oxygenation.
   - D. Heliox cannot be used in this child because of the high oxygen requirement and the inability to provide a significant fraction of helium.
   - E. Heliox is a reasonable alternative as it will also lower pulmonary vascular resistance.

3. *The monitoring of serial arterial blood gases may be useful in which of the following upper airway obstruction scenarios?*
   - A. A 14-month-old with sudden onset of cough and stridor while playing with a Lego building set with his 4-year-old sibling.
   - B. An 18-month-old with acute laryngotracheobronchitis.
   - C. A 4-year-old with acute epiglottitis while considering whether to transport to a tertiary care children's hospital prior to intubation.
   - D. A 6-year-old with static encephalopathy requiring nocturnal BiPAP who has worsening upper airway obstruction during an acute upper respiratory infection.
   - E. A 5-year-old with peanut allergy with acute upper airway obstruction after exposure to nuts to assess the response to an injection of epinephrine.

4. *Which of the following statements is true regarding the administration of supplemental oxygen to children with and upper airway obstruction?*
   A. Supplemental oxygen should be administered to avoid hypoxemia; however, its use mandates periodic blood gas analysis (arterial or venous) to assess for evidence of hypoventilation and hypercapnia.
   B. Supplemental oxygen administration can exacerbate atelectasis in the child with laryngotracheitis, and, therefore, the lowest possible concentration of oxygen that maintains the pulse oximeter reading just above 90% should be administered.
   C. Supplemental oxygen should be readily administered because the threat to life from upper airway obstruction comes from hypoxemia and cardiac arrest.
   D. Supplemental oxygen administration can mask hypoventilation and hypercapnia in the child with laryngotracheitis, and, therefore, its use should be avoided to allow for more effective monitoring of the patient.
   E. Supplemental oxygen should *not* be administered via positive pressure systems (i.e., high-flow nasal cannula, continuous positive airway pressure, bi-level positive airway pressure) because the positive pressure may displace the epiglottis posteriorly exacerbating airway obstruction.

5. *Which of the following statements is true regarding differences in the airway anatomy and physiology between the infant and the adult?*
   A. The infant possesses a relatively larger tongue in contrast to the adult.
   B. The infant airway is relatively longer than that of the adult.
   C. The narrowest portion of the airway of the infant is at the vocal cord opening.
   D. The oxygen consumption (mL/kg/min) of the infant is approximately half that of the adult.
   E. The infant airway is more posterior and caudal relative to the adult.

6. *The primary disadvantage of the use of a laryngeal mask airway (LMA) is which of the following?*
   A. The proper utilization of the LMA requires individuals with extensive training in the technique.
   B. The LMA is associated with a greater potential for airway trauma and stress than a laryngoscopic intubation in the hands of individuals trained for either procedure.
   C. The LMA is unable to fully protect the respiratory tract from aspiration in the event of vomiting.
   D. The LMA is placed with insertion by hand into the pharynx, and, therefore, airway anatomy is not visualized.
   E. The LMA has limited use in the airway management of small children because of differences in their airway from the adult.

7. *A 6-month-old male with Pierre Robin sequence presents with signs and symptoms of viral bronchiolitis. He is admitted to the PICU with increased work of breathing and with mild hypoxemia (SpO_2 92%). He is placed on continuous positive airway pressure (CPAP) via nasal prongs with improved oxygenation and decreased work of breathing. You are called to the bedside for an acute deterioration (SpO_2 78%) requiring bag-mask ventilation. The oxygenation improves in response to the bag-mask ventilation. What is the most appropriate next intervention?*
   A. Continue bag-mask ventilation and prepare for intubation using ketamine sedation.
   B. Administer heliox via the CPAP circuit.
   C. Convert the CPAP to bi-level positive airway pressure (BiPAP).
   D. Discontinue bag-mask ventilation and monitor to assess if he is able to maintain adequate oxygenation.
   E. Continue bag-mask ventilation while mobilizing difficult airway personnel and equipment.

8. *A 2-year-old male develops pneumococcal pneumonia complicated by empyema and ARDS. He is currently intubated with a 4.5 cuffed ETT and is being weaned from mechanical ventilation. He has a respiratory rate is 24–30 breaths per minute and has spontaneous tidal volumes of 7 ml/kg while on pressure support of 5 cm H_2O. His FiO_2 is 30%, and he is saturating 98%. He is extubated on day 18 after successful spontaneous breathing trials. Within 30 min of extubation, he develops stridor and increased work of breathing. He has an acute desaturation to 50% and requires emergent reintubation. His vocal cords are easily visualized using GlideScope videolaryngoscopy, but the ETT cannot be passed easily through the cords. A 3.5 cuffed ETT is passed on the third attempt. Which of the following is true?*
   A. The child should have undergone an ETT leak test. The lack of a leak would have been highly predictive of extubation failure.
   B. The child has developed subglottic stenosis as a result of concomitant pneumococcal bacterial tracheitis.
   C. The child has developed subglottic stenosis as a result of prolonged intubation with a cuffed tube, and definitive treatment is a tracheostomy.
   D. The child has developed subglottic stenosis which is far more common in neonates after prolonged intubation.
   E. The child developed subglottic stenosis as a result of multiple contributing factors which may have included undersedation during prolonged mechanical ventilation.

Answers

1. B
2. B
3. D
4. C
5. A
6. C
7. E
8. E

Suggested Readings

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Severe Asthma

Ronald Wong and Frank A. Maffei

Contents

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Learning Objectives

- Discuss the impact of asthma on the pediatric population
- Review the pathophysiology of status asthmaticus
- Review the usual triggers of asthma and appreciate potential iatrogenic triggers of bronchospasm in the PICU
- Describe the evaluation of a child admitted to the PICU with status asthmaticus
- Outline a tiered treatment algorithm for asthmatic patients requiring critical care
- Review the major tiered therapies for status asthmaticus
  - Inhaled beta-agonists
  - Inhaled anticholinergic agents
  - Corticosteroids
  - Magnesium
  - Helium/oxygen mixture
  - Intravenous beta-agonists
  - Methylxanthines
  - High-flow nasal cannula
  - Noninvasive ventilation
  - Mechanical ventilation
  - Ketamine
  - Inhalational anesthetics
  - ECMO
- Mechanical ventilation strategies in severe asthma
  - Review the theoretical and practical difficulties with mechanical ventilation in patients with status asthmaticus
  - Discuss the complications that may occur with status asthmaticus during positive pressure ventilation

10.1 Introduction

Asthma remains one of the most common chronic childhood diseases. Asthma affects nearly 7 million children and is a frequent cause of emergency department visits and hospitalizations. Over the past few decades, the prevalence of childhood asthma has increased at a rate of 1.4% per year. For the period 2008–2010, average annual prevalence was higher in children <18 years of age (9.5%) compared to adults (7.7%) (Fig. 10.1). Population-based asthma exacerbation prevalence rates were higher in children (range 5.2–5.8%) as compared with adult rates (range 4.4–5.4%).

The majority of children with asthma can be safely managed in the outpatient setting using preventative measures which include trigger avoidance and compliance with controller medications. However, a small subset of children may have severe asthma with recurring exacerbations that, at times, may be life-threatening (status asthmaticus). Although severe asthma likely affects less than 5% of all asthmatic children in the United States, the resource utilization of patients with severe pediatric asthma is disproportionate to disease prevalence. Annual total medical expenditures of childhood asthma are estimated at greater than $10 billion, with severe asthma accounting up to 50% of those costs.

Status asthmaticus is defined as an asthma exacerbation that does not respond to first-tier therapy (nebulized beta-agonists, nebulized anticholinergics, and system corticosteroids) requiring inpatient admission. Children with status asthmaticus are at risk of progressing to respiratory failure.

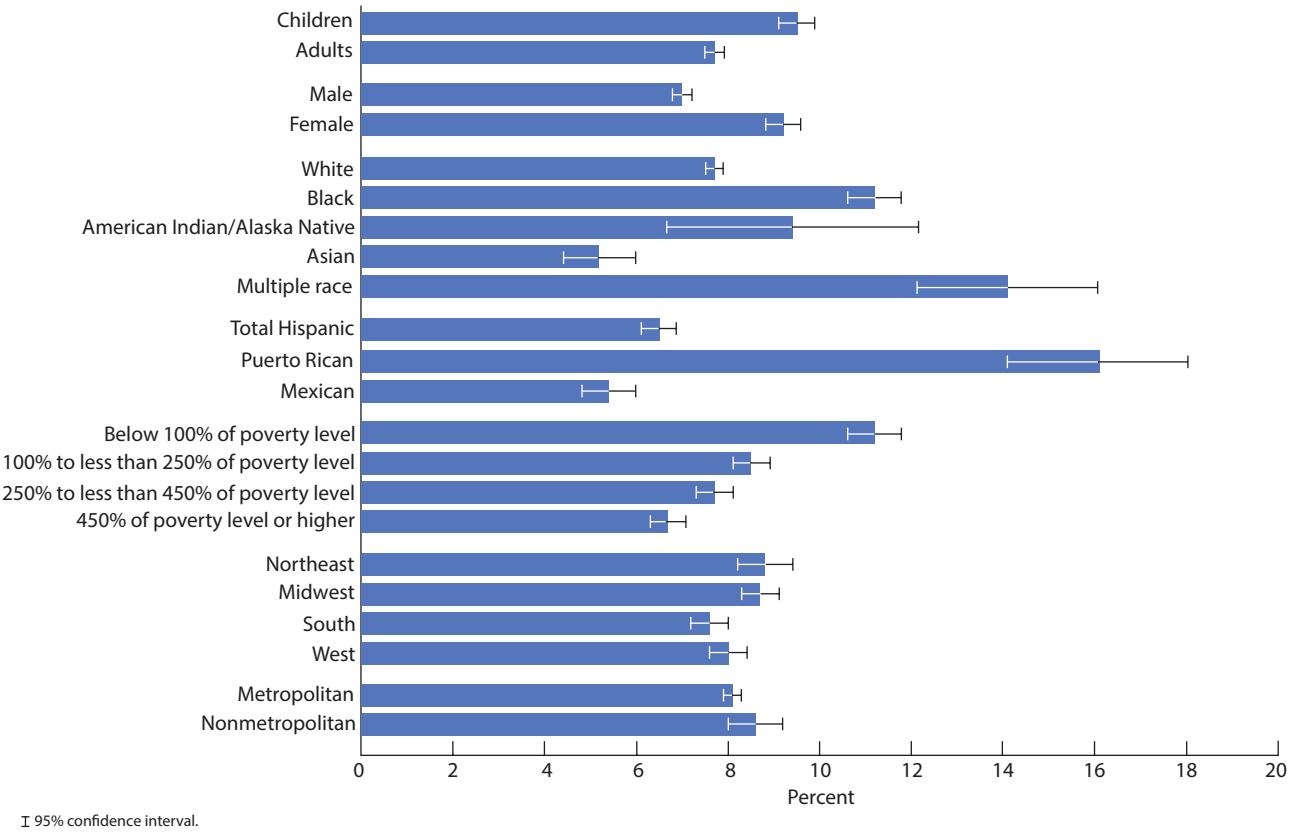

Fig. 10.1 Current asthma prevalence, by age group, sex, race and ethnicity, poverty status, geographic region, and urbanicity: United States, average annual 2008–2010. (Source: CDC/NCHS, National Health Interview Survey and Health Data Interactive)

Diagnosing and managing severe asthma require an understanding of the underlying pathophysiologic framework. Asthma is a complex heterogeneous inflammatory disorder that is characterized by variable and recurring symptoms of airflow obstruction due to inflammation, bronchospasm, and mucous plugging. Multifactorial interactions between host (polygenetic) and environmental factors determine clinical manifestations, severity of asthma, and response to treatment (Fig. 10.2).

10.2 Genetic Factors

Although inheritable factors are clearly important, it is unlikely that a single gene is responsible for the various asthma phenotypes. Children with a family history of asthma are at increased risk of developing asthma, but transmission of the disorder does not follow simple Mendelian inheritance. Several genes (polygenic) interacting with each other offer a more plausible explanation. Several candidate genes have been proposed through genetic linkage analysis, genetic association analysis, and genome-wide association studies. These studies confirm that asthma is both a genetically and phenotypically heterogeneous disorder.

A growing list of over 100 genes has been associated with asthma. For example, a disintegrin and metalloproteinase 33 (ADAM33) gene is located on chromosome 20p13, and the protein is expressed in bronchial smooth muscle cells and lung fibroblasts. It is shown to be strongly linked to asthma, bronchial hyperresponsiveness, and airway remodeling.

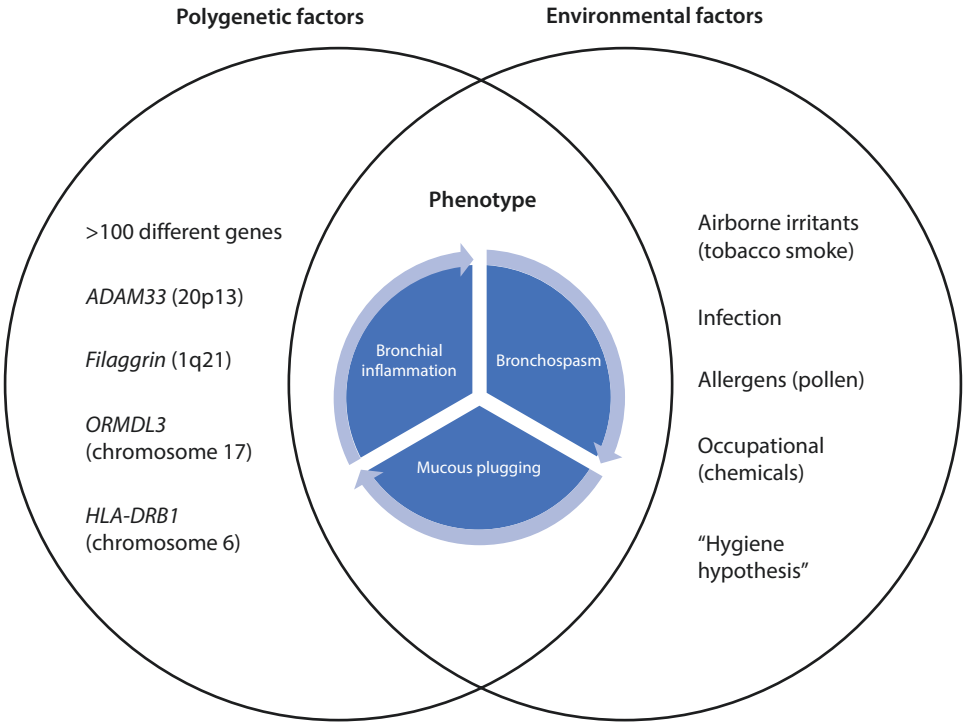

Fig. 10.2 Multifactorial interactions resulting in the pathophysiologic symptoms of asthma

10

The phenotype of asthma is likely due to a complex multifactorial gene-environment interaction.

Filaggrin is a protein involved in maintaining an effective skin barrier. The gene is located on chromosome 1q21, and loss-of-function mutations are associated with the development of allergic sensitization, hay fever, and asthma. That development only occurred in patients with atopic dermatitis. Dysfunction of the skin barrier enhances sensitization to allergens and leads of systemic allergic responses including increased IgE levels and airway hyperresponsiveness. It appears that absorption of allergens through the skin of patients with this loss-of-function mutation is a prerequisite for the development of asthma. The importance of polygenetic interactions leading to the development of asthma should not be underestimated.

Asthma genome-wide association studies (GWAS) are used to identify single-nucleotide polymorphisms (SNPs) across the genome. The GABRIEL consortium, a large-scale GWAS of asthma, reports associations between asthma and numerous SNPs found on chromosomes 2, 6, 9, 15, 17, and 22. There are multiple makers on chromosome 17q21 strongly associated with childhood-onset asthma. Variation in the expression of *ORMDL3* (17q21), a member of a gene family that encodes transmembrane proteins, contributes to the risk of childhood asthma. *GSDMB* (17q21) also demonstrates a strong genetic linkage to asthma. It is highly expressed in lung bronchial epithelium and regulates airway remodeling and hyperresponsiveness. While genetic factors play an important role in the development and severity of asthma, further study is necessary to delineate the clinical importance of these genes and their polymorphisms especially as they relate to the clinical response to pharmacological treatments.

10.3 Environmental Factors

Numerous theories have been considered to explain the increase in asthma prevalence. Many of which continue to be sharply debated. One hypothesis is based on the apparent association between exposure to irritants (e.g., second-hand

tobacco smoke, viruses, and pollen) and the subsequent development of asthma in childhood. This theory can be extended to early infection with respiratory syncytial virus which has been linked to the development of asthma. However, this theory is speculative, as it is unclear whether the exposure to an asthma trigger during a time of rapid lung growth leads to airway remodeling or whether the respiratory symptoms that occur with these early exposures are simply the initial presentation of a child who is "prone" to the development of asthma.

In contrast, the "hygiene hypothesis" postulates that increased hygienic conditions and declining family size in industrialized nations have led to reduced microbial exposure in early childhood. The functional counter-regulatory T cell subsets, T helper 1 (TH1) and T helper 2 (TH2), have provided the immunologic paradigm to study this hypothesis. The paradigm suggests that reduced microbial exposure early in life directs the maturing immune system toward proallergic TH2 responses and suppresses counter-regulatory TH1 imprinting. TH2 is critical in cytokine production including interleukin (IL)-4, IL-5, IL-9, and IL-13. These cytokines mediate the initiation, maintenance, and amplification of cellular inflammation in the asthmatic lung.

The immunologic paradigm also emphasizes the importance of regulatory T (Treg) cell classes. Treg cells may dampen allergen-specific TH2 responses, and the lack of stimulation of the immune system reduces activation of Treg cells. Despite extensive study, it is unlikely that the hypothesis alone can explain the increase in asthma prevalence.

Asthma prevalence continues to increase, but the etiology of this increase is still unknown.

10.4 Triggers of Asthma

There are many known stimuli that can incite severe asthma exacerbations. The most well-understood mechanism is *IgE-mediated allergic asthma*. This immediate type of hypersensitivity occurs when IgE molecules bound to resident mast cells interact with the allergic antigen and lead to the inflammatory response governed by lymphocytes. This stimulus can lead to immediate airway obstruction that is generally short-lived but may be followed by a late reaction which can be more severe and persistent.

While *infections* from both viral and bacterial sources can trigger severe asthma in children, viruses appear to be the major infectious trigger. In the very young child, respiratory syncytial and parainfluenza virus predominate, while in older children, influenza and rhinovirus become more prevalent. Human metapneumovirus and bocavirus have recently been implicated in viral-induced asthma exacerbations in children.

In all age groups, but particularly noteworthy in infants, *gastroesophageal reflux disease* can produce bronchospasm. The etiology is likely due to direct irritation of the airways by refluxed gastric material or, alternatively, by neurally induced bronchospasm secondary to irritation of vagal nerve fibers located in the distal esophagus. The control of reflux and gastric acidity remains an important component of asthma treatment.

Environmental irritants including air pollution and second-hand smoke may predispose children with bronchial hypersensitivity to severe asthma exacerbations. In children, second-hand smoke from caretakers is known to play a major role in triggering asthma and may contribute to the severity of the exacerbation.

In addition to the aforementioned triggers for asthma, older children and adolescents may have asthma induced by exercise, emotional stress, cigarette smoking, and inhalant abuse.

Exercise is a common trigger of severe asthma, especially in the adolescent. The worsening of airway obstruction may occur after exercise and not during it. Pretreatment with inhaled therapies may have some success in preventing exacerbations of exercise-induced asthma.

Bronchoconstriction secondary to vagal efferent nerve activity can also be triggered by *emotional stress* in the older child. This trigger is particularly important when tailoring treatment for a child requiring intensive care. It is possible that an external stimulus may initiate an exacerbation, but increasing emotional distress can worsen its severity. Therefore, the judicious use of low-dose sedation may be required in children admitted to the PICU with status asthmaticus who are not mechanically ventilated.

There are many external triggers of asthma that require careful assessment by history upon PICU admission. Common triggers include IgE-mediated allergic asthma, infections, air pollution, exercise, and GERD.

At times, a trigger for a severe asthma exacerbation cannot be readily identified. Symptoms can appear abruptly and progress quickly. A rapid-onset, severely progressive form of asthma exacerbation in older children has been appreciated. Acute asphyxial asthma (AAA), or rapid-onset near-fatal asthma, is well described in adults. AAA has a predilection for young adult males and is characterized by a brief duration of symptoms (usually less than 6 h), few identifiable triggers, and a rapid progression to respiratory failure. Often, the patient will present in extremis, cyanotic, with little to no air movement, and obtundation. Despite the severity of presentation, response to therapy is prompt. When mechanical ventilation is warranted, its duration is usually short, due to rapid improvements in gas exchange. The pathophysiology of AAA may be distinct. An initial neurogenic event that mediates intense bronchospasm may be of primary importance and be independent of the submucosal cellular profile.

Iatrogenic triggers of bronchospasm include medications, airway manipulation (e.g., bronchoscopy), and mechanical ventilation. Medications that are of particular importance are beta-adrenergic antagonists. These agents have been demonstrated to incite bronchospasm and should be avoided or used with caution in a child with a known history of asthma. Cardio-selective beta-1 adrenergic antagonists may induce less bronchospasm but should still be used with caution. Other agents such as aspirin, nonsteroidal anti-inflammatory drugs, and sulfating agents can also incite bronchospasm. Children with a history of asthma are at increased risk for developing bronchospasm after the initiation of mechanical ventilation for processes unrelated to the lungs (e.g., neurologic or cardiovascular support).

10.5 Pathophysiology

Despite the many triggers of status asthmaticus, the underlying pathophysiology remains constant and is composed of three mechanisms: *bronchial inflammation/edema*, *airway smooth muscle spasm* (bronchospasm), and *airway mucous plugging*. All these mechanisms lead to a reduction in airway diameter, increased airway resistance, and severe airflow obstruction.

10.5.1 Inflammation

Even in asymptomatic asthmatic children, the airway is in a state of low-grade persistent inflammation.

Bronchial inflammation induced by resident airway inflammatory cells or infiltrating inflammatory cells characterizes asthma. Children with severe asthma, even when asymptomatic, have airways that are in a state of low-grade persistent inflammation. Although a variety of inflammatory cells contribute to this airway inflammation, cells most active during an acute exacerbation include infiltrative lymphocytes, eosinophils, resident mast cells, and airway epithelial cells.

During asthma exacerbations, *lymphocytes* (specifically the TH2 subtype) are drawn to infiltrate the airway by signaling from a variety of chemokines, with eotaxin being the most studied. Once activated, lymphocytes

release a host of inflammatory cytokines (e.g., IL-4 and IL-5) that further stimulate the inflammatory response, leading to increased edema. Other inflammatory mediators, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), regulated on activation, normal T cell expressed and secreted (RANTES), and IL-8, contribute to the ongoing inflammatory response that occurs during status asthmaticus.

Eosinophils play a major role in this upregulated inflammation, leading to release of leukotrienes and the formation of oxygen free radicals, all of which worsen airway edema and mucus production. A study of adults with asthma demonstrated that the number of eosinophils found in bronchoalveolar lavage fluid is directly proportional to asthma severity.

Lymphocytes and eosinophils are important infiltrative cells in asthma pathogenesis.

Mast cells are resident airway cells that are upregulated when stimulated by allergens. Activation occurs after an allergen binds with an IgE antibody attached to the mast cell surface. Once induced, mast cells are pro-inflammatory and release a variety of granule-associated mediators including histamine, proteases, and cytokines. Mast cell activation also induces de novo synthesis of leukotrienes. IgE-mediated mast cell activation is an important component of the inflammatory response in asthma and has become a therapeutic target. A humanized IgG monoclonal antibody (omalizumab) has been developed which binds circulating IgE. Once bound to the monoclonal, IgE can no longer associate with mast cell surface receptors, and thus activation and degranulation are inhibited. Omalizumab has been proven as an effective maintenance therapy to prevent allergen-induced asthma exacerbations in children older than 6 years with poorly controlled asthma. However, it currently does not have a role in acute exacerbations.

Airway epithelial cells produce several cytokines and chemokines that regulate inflammation during severe asthma. IL-1-beta is the most intensely studied. Bronchoalveolar lavage fluid IL-1-beta concentrations have been correlated with asthma severity in adults. The IL-1-beta inflammatory pathway has been manipulated in attempts to gain control over the inflammatory response that triggers worsening asthma with some success in vitro.

Mast cells and airway epithelial cells are important resident cells in asthma pathogenesis.

Given the importance of inflammation, some experts suggest that methods to noninvasively measure inflammation may have a role in chronic asthma therapy. An inflammatory product that is increased and readily measurable is exhaled nitric oxide (NO). L-arginine and L-citrulline are oxidized by NO synthases (NOS), which synthesize NO. The measurement of fraction of exhaled NO (FeNO) has become a useful clinical point-of-care marker of inflammation in asthma. The FeNO has been found to decrease after steroid therapy in asthmatics. It has also been found to be useful in predicting asthma exacerbations in adults.

The fraction of exhaled nitric oxide may be a clinically useful marker for airway inflammation in children with asthma.

10.5.2 Bronchospasm and Airway Resistance

The airway smooth muscle (ASM) cell is the end effector of bronchospasm. Airways may constrict too much (airway hyperresponsiveness) or too easily (airway hypersensitivity) in response to a trigger. Although airway hyperresponsiveness and hypersensitivity have been described empirically in asthmatics, the underlying mechanisms are not fully elucidated. It is thought that remodeling leading to increased ASM mass is the primary derangement as opposed to decreased load against which the ASM must contract. Increasing evidence suggests that the bronchodilating response to periodic stretch and deep inspirations is impaired in asthma leading to ASM to be shortened and frozen in a "latch" state (Fig. 10.3).

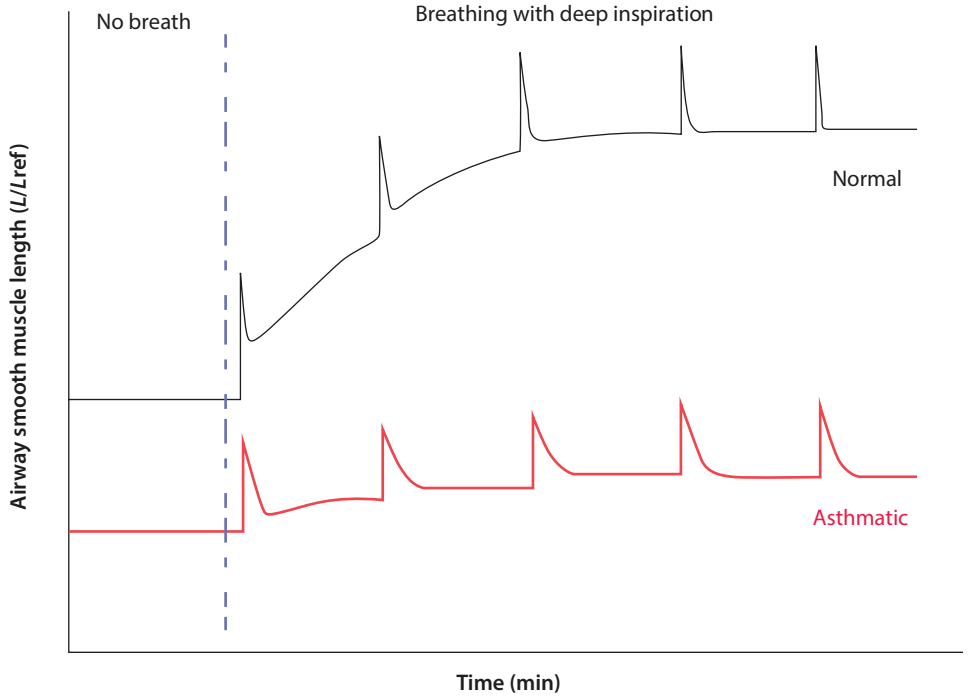

Fig. 10.3 In vitro airway smooth muscle length (averaged over duration of one breath) vs time. The normal airway remains dilated in response to deep inspiration, while the asthmatic airway only dilates by a smaller amount and returns to a static constricted state

The three mechanisms responsible for airway obstruction in asthma are bronchial mucosal inflammation/edema, airway smooth muscle spasm (bronchospasm), and airway mucus plugging from copious secretions.

Decreasing the airway radius by 50% leads to a 16-fold increase in resistance.

As the diameter of pediatric airways is proportionally smaller than an adult, a child has greater vulnerability to bronchospasm and, therefore, more likely to demonstrate symptoms of respiratory distress. At times, this distress can have an abrupt onset and rapid progression.

The effect of a reduction in airway diameter is best appreciated when considering Poiseuille's equation, which states:

$$R = 8\eta L$$

where R = resistance, η = viscosity of the air (or fluid), L = length of the tube (airway), and r = radius of the tube (airway).

Accordingly, decreasing the radius by 50% (as can occur readily in the small airway of a child) will result in a 16-fold increase in airway resistance.

10.5.3 Mucous Production

Mucous hypersecretion has long been recognized as a significant component of airway obstruction in asthma. Increased mucous production coupled with impaired clearance can significantly worsen airway obstruction in asthma. Recently, improved understanding has evolved regarding the pathophysiology of mucous production during asthma exacerbations.

In the nonpathological state, airway epithelium is covered by a mucus gel layer approximately 5–50 μm thick. Ciliary motion within this layer promotes movement of mucous proximally to the pharynx where it is swallowed together with entrapped particles and pathogens. MUC5B is the principal gel-forming mucin produced during homeostasis and provides this essential particle clearance function.

Inflammation in asthma induces airway epithelial remodeling and changes in intracellular mucin production. Under pathological conditions, mucin secretion

increases, and its composition changes. There is an increase in goblet cell number (hyperplasia) and a phenotypic change in the mucin-producing cells (metaplasia). This transformation results in a dramatic increase in the production of MUC5AC, the principal mucin upregulated during asthmatic inflammation. A proposed pathologic mechanism of MUC5AC mucin is its ability to increase tethering of mucous to the luminal epithelium causing accumulation of mucous and increased plugging.

Studies have demonstrated that concentrations of MUC5AC are elevated compared to MUC5B in individuals with asthma. In children, a similar high ratio of MUC5AC to MUC5B has been noted. Interestingly, increased MUC5AC has been found in children with both stable and acute asthma versus healthy controls. Currently, there is no convincing evidence for the use of mucolytics or agents that inhibit mucous production in children with asthma exacerbations. However, MUC5AC gene transcription or MUC5AC goblet cell differentiation may provide future therapeutic targets.

10.5.4 Cardiopulmonary Interactions

It is important to consider the pathophysiology of cardiopulmonary interactions that occur during asthma exacerbations. Pulsus paradoxus, the expected small decrease in systolic blood pressure during inspiration, can be greatly accentuated during forceful inspiration and the air trapping seen in severe asthma. These amplified interactions can have profound hemodynamic effects.

A deleterious cycle (Fig. 10.4) leading to a biventricular increase in afterload and relative reduction in preload can occur during severe asthma.

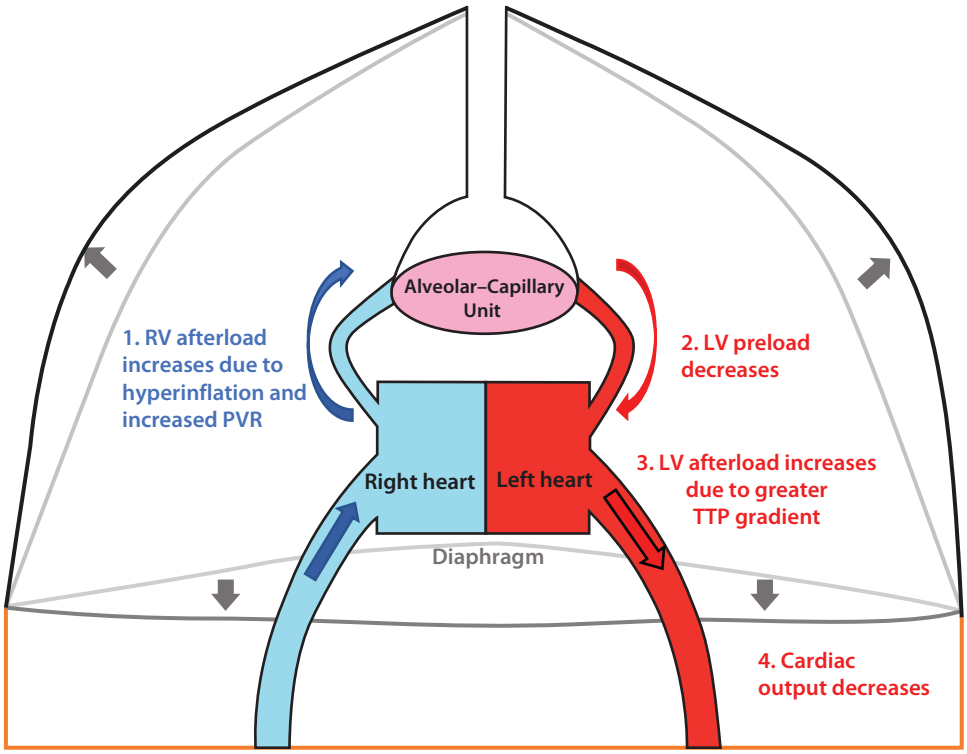

Fig. 10.4 Cardiopulmonary interactions during severe asthma. Air trapping leads to dynamic hyperinflation and diaphragmatic flattening (gray arrows). Right ventricular afterload increases due to hyperinflation-induced compression of alveolar vessels and hypoxia-induced increased PVR. Pulmonary venous return is compromised, and left heart preload is reduced. RV preload may also be decreased due to poor intake and increased insensible losses. LV afterload increases due to greater transthoracic gradient. The net effect of these hemodynamic changes can lead to a reduction in cardiac output. *RV* right ventricle, *PVR* pulmonary vascular resistance, *LV* left ventricle, *TTP* transthoracic pressure

Forceful negative pressure inspiration and ongoing expiratory obstruction lead to dynamic hyperinflation. Hyperinflation and hypoxia lead to an increase in pulmonary vascular resistance and right ventricular afterload. Left atrial filling and left ventricular (LV) preload are subsequently reduced.

The effect on left ventricular afterload is of particular importance. During forceful inspiration, the intrathoracic pressure (ITP) surrounding the left ventricle decreases markedly, while the pressure surrounding the extra-thoracic arterial compartment remains constant. LV afterload increases as the left ventricle must overcome a greater pressure gradient to eject blood. Increased LV afterload combined with decreased LV preload can severely compromise LV ejection and reduce cardiac output.

Additionally, children may present with hypovolemia secondary to increased insensible losses and poor fluid intake. Tachycardia secondary to stress, hypovolemia, and bronchodilators may further reduce ventricular filling time and preload.

These cardiopulmonary interactions place the asthmatic child in a tenuous hemodynamic state. Cardiac output can be reduced at presentation or may progressively decline after the institution of positive pressure ventilation. Although positive pressure can reduce LV afterload, the institution of positive pressure in the failing asthmatic can dramatically reduce RV preload, thus negating any favorable effects on LV afterload. In addition, medications used for intubation often are cardiac depressants. Medication effects coupled with a sudden reduction in right heart preload can produce profound hypotension. If intubation seems imminent, appropriate volume expansion is often necessary to reduce the risk of hemodynamic instability.

10.6 Evaluation of Status Asthmaticus

A severe asthma exacerbation, also termed "status asthmaticus," is characterized by a lack of response to repetitive or continuous administration of short-acting inhaled beta-2 adrenergic receptor agonists and steroids. Exacerbations can be variable in severity and response to treatment.

The initial assessment of exacerbation severity is based on a thorough *examination* of the child. A visual assessment of work of breathing may reveal accessory muscle use, paradoxical thoracoabdominal breathing, and nasal flaring. Expiratory wheezing is commonly heard and can be graded as mild, moderate, or severe. The absence of wheezing may signify severe airflow obstruction. Expiratory prolongation is common and may be truncated due to air trapping. Cerebral function should be monitored closely as children with carbon dioxide retention or hypoxia may exhibit alterations in mental status such as agitation or lethargy. Lethargy, inability to phonate, cyanosis, and a silent chest are ominous signs that often precede respiratory arrest.

An underappreciated examination finding is the presence and severity of a *pulsus paradoxus*. When measured in a normal child, the decrease in systolic blood pressure during inspiration is generally 5 mmHg. In moderate asthma, a decrease of 10–20 mmHg is often noted. A systolic pressure decrease of >20 mmHg during inspiration is seen in children with severe exacerbations. The hemodynamic impact of this accentuation has been previously discussed.

Serial physical examinations remain the cornerstone for the ongoing assessment of the child with severe asthma. Using a validated scoring system allows the clinician to objectively assess the response to treatment and adjust interventions accordingly. As with any clinical scoring tool, interobserver

variability and the subjective nature of some variables may limit the clinical usefulness of certain tools.

Several reliable clinical scoring systems have been developed to help gauge the severity of asthma exacerbation, including the Pediatric Asthma Score (PAS), Wood-Downes asthma score, Becker asthma score, Acute Asthma Intensity Research Score, and Pediatric Pulmonary Index Score. The Pediatric Asthma Score is outlined in ◘ Table 10.1. The clinical asthma score allows multiple caregivers to assess progression or improvements in a child with severe asthma.

Serial clinical examinations are of paramount importance in the child with severe asthma.

Measurement of expiratory airflow with a peak flow meter is very useful in older children who can reliably perform this maneuver. This measurement is safe and inexpensive, and it also can be performed repeatedly, allowing the clinician to assess therapy effectiveness.

A *chest radiograph* (◘ Fig. 10.5) allows the clinician to detect hyperinflation, concomitant pneumonia, pneumothorax, or pneumomediastinum. A large pneumothorax warrants chest tube or pigtail catheter placement. In a mechanically ventilated child, the radiograph is also used to determine appropriate depth of the endotracheal tube.

An *arterial blood gas* will aid in determining alterations in gas exchange but must be interpreted in the context of the clinical examination. A $PaCO_2$ of greater than 45 mmHg in a child with a severe asthmatic exacerbation likely warrants PICU admission and serial arterial blood gas monitoring. In a child with severe tachypnea, increasing work of breathing, and hypoxia, a "normal" $PaCO_2$ may not be physiologically appropriate and indeed may signify worsening gas exchange. Clinical symptoms, such as the ability to speak, mental status, and diaphoresis, are likely as reliable if not more reliable to determine respiratory failure when compared to arterial blood gas data.

It is important to remember the old adage, "All that wheezes is not asthma," and clinicians should consider alternative diagnoses. The differential diagnosis of lower airway obstruction includes tracheomalacia and bronchomalacia (especially in children less than 2 years of age), cystic fibrosis, viral bronchiolitis, for-

◘ **Table 10.1** Pediatric asthma score

Pediatric asthma score (PAS)	1	2	3
	Respiratory rate		
2–3 years	≤ 34	35–39	≥ 40
4–5 years	≤ 30	31–35	≥ 36
6–12 years	≤ 26	27–30	≥ 31
>12 years	≤ 23	24–27	≥ 28
Oxygen requirements	>95% on room air	90–95% on room air	<90% on room air or on any oxygen
Auscultation	Normal breath sounds to end-expiratory wheeze only	Expiratory wheezing	Inspiratory and expiratory wheezing to diminished breath sounds
Retractions	None or intercostal	Intercostal and substernal	Intercostal, substernal, and supraclavicular
Dyspnea	Speaks in sentences, coos, and babbles	Speaks in partial sentences, short cry	Speaks in single words/short phrases/grunting

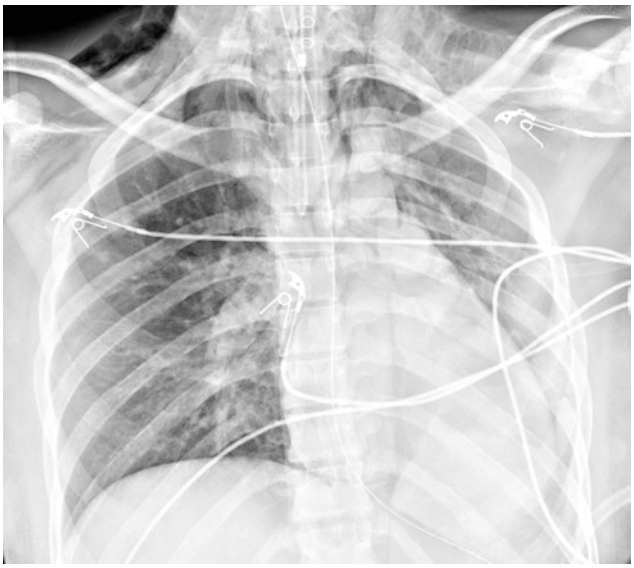

Fig. 10.5 Post-intubation findings on chest radiograph of a teenager with status asthmaticus include hyperinflation, left-sided subsegmental atelectasis, and air leaks which lead to pneumomediastinum and subcutaneous air

eign body aspiration (usually a sudden onset of wheezing in a previously healthy child), cardiac wheezing secondary to congenital heart disease or myocardial failure, viral croup, bacterial tracheitis, psychogenic wheezing, and vocal cord dysfunction. Congenital fixed anatomic obstructions can also mimic bronchiolitis and asthma, especially in the first year of life. These include vascular rings, airway hemangiomas, and tracheal webs. A thorough history and physical examination will often exclude many of these disorders that can mimic severe asthma.

Vocal cord dysfunction can be challenging to differentiate from lower airway obstruction, and episodes have been mistakenly treated as a severe asthma exacerbation. Vocal cord dysfunction (VCD) is defined as the paradoxical adduction of vocal cords during inspiration. It may be precipitated by emotional stress, exercise, and extrinsic or intrinsic irritants. All of which are known triggers for an asthma exacerbation. VCD tends to present as exertional dyspnea in an adolescent female. Differentiating VCD from asthma based on history alone is often not possible. Examination findings suggestive of VCD include auscultation of inspiratory wheezing or stridor over the larynx and a lack of hypoxia. Diagnosis of VCD can be made using pulmonary function testing confirming extra-thoracic inspiratory obstruction or, more definitively, with direct visualization of inspiratory adduction of vocal cords through fiberoptic rhinolaryngoscopy.

10.7 Treatment Algorithm for Severe Asthma in Children

Asthma therapy must be tailored for each child, considering disease severity, response to therapeutics, and adverse effects of therapies.

Asthma therapy in the PICU must be tailored to disease severity, age, comorbidities, host response, and adverse therapeutic effects. Figure 10.6 outlines a general algorithm for the treatment of severe asthma in children. The key to the treatment of severe asthma is reassessment after each therapeutic intervention, noting both efficacy and adverse events. The algorithm outlines possible therapeutic strategies.

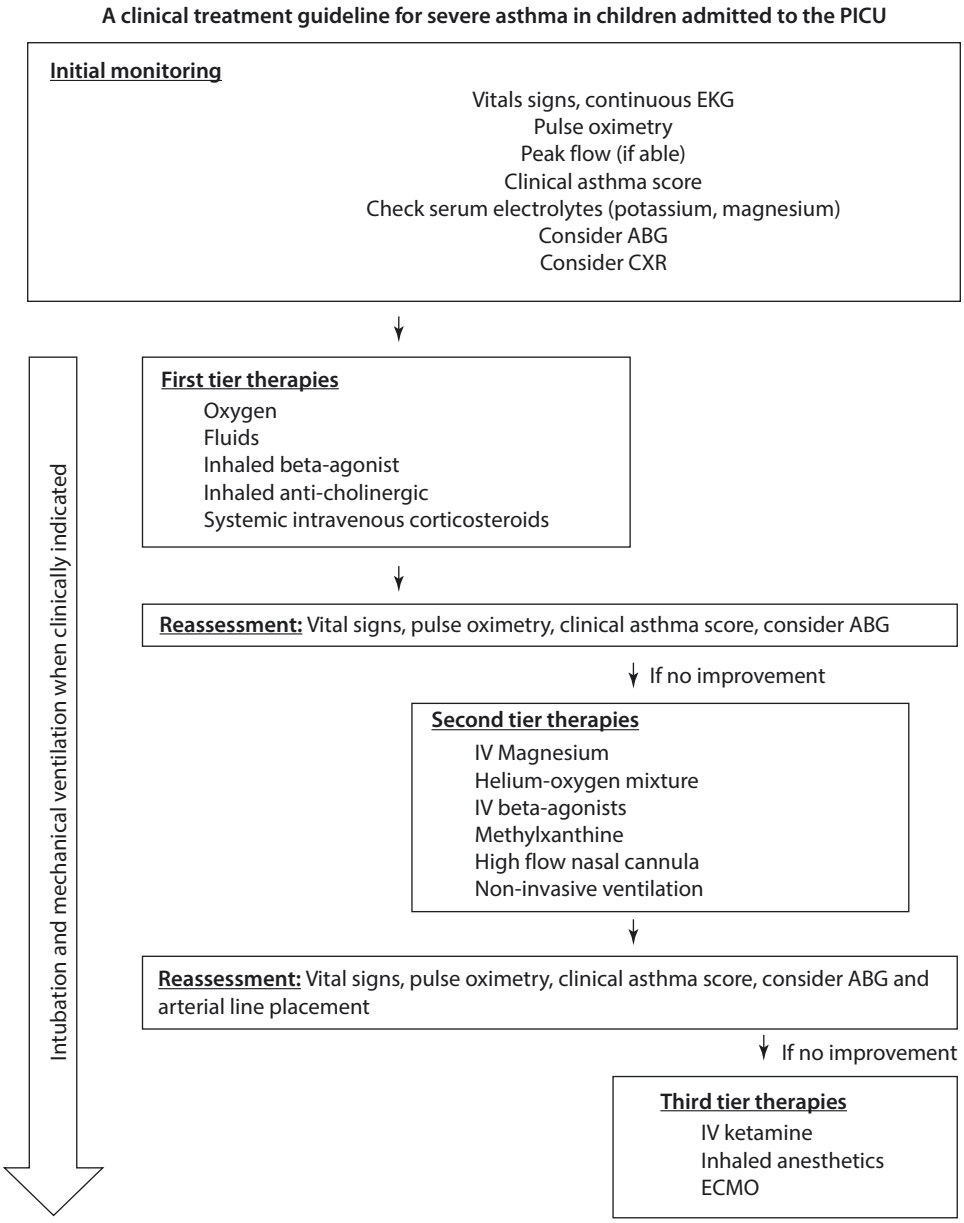

Fig. 10.6 Algorithm for the step-wise approach to escalating therapy in acute asthma

10.8 Therapies for Status Asthmaticus (Table 10.2)

10.8.1 First-Tier Therapies

10.8.1.1 Oxygen

Oxygen delivery is the key treatment goal in caring for a child with severe asthma.

Avoidance of hypoxia remains the primary goal in status asthmaticus. Ventilation/perfusion mismatch routinely develops with severe asthma due to air trapping, atelectasis, and mucous plugging. Contrary to adults with chronic obstructive pulmonary disease, supplemental oxygen will not suppress the respiratory drive in children with asthma. Therefore, oxygen therapy at high concentrations can be administered. Refractory hypoxia is the

Table 10.2 Tiered medications for severe asthma

	Mechanism of action	Adverse effects
First-tier therapy		
Inhaled beta-agonists	Bronchodilation: Stimulation of beta-2 receptors leading to bronchodilation by adenosine 3′,5′-cyclic monophosphate (cAMP)	Stimulation of beta-1 that can result in tachycardia Excitability/hyperactivity Tremor Hypokalemia
Inhaled anticholinergics	Bronchodilation: Inhibits parasympathetic-mediated bronchoconstriction by blocking muscarinic receptors of acetylcholine	Pupillary dilation if agent comes in contact with the eye
IV Corticosteroids	Anti-inflammatory	Glucose intolerance Peptic ulcer Long-term therapy: Suppression of hypothalamic-pituitary-adrenal axis, bone demineralization, myopathy, growth failure
Second-tier therapy		
IV Magnesium	Bronchodilation: Inhibits calcium intake into airway smooth muscle cells	Hypotension Flushing Arrhythmia Weakness CNS depression
Helium/oxygen mixture	Biologically inert gas that reduces Reynolds number thus favoring laminar flow	Patients with oxygen requirements may not tolerate helium/oxygen mixture
IV Beta-agonists	Bronchodilation: Same as inhaled beta-agonists	Tachycardia/dysrhythmias Cardiac ischemia
Methylxanthines	Bronchodilation: 1. Non-selective inhibitors of phosphodiesterases thus increasing intracellular cAMP and downregulating pulmonary cell inflammatory burst 2. Inhibition of adenosine-induced bronchoconstriction	Nausea/emesis Agitation Tachycardia Toxic levels: Urinary retention, arrhythmias, irritability, seizure
Third-tier therapy		
IV Ketamine	Bronchodilation (possible mechanisms): 1. Catecholamine release stimulating beta-2 adrenergic receptors 2. Inhibition of vagal pathways to produce anticholinergic effect on bronchial smooth muscle	Hallucinations Bronchorrhea Laryngospasm Tachycardia Hypertension Seizures
Inhaled anesthetics	Bronchodilation (possible mechanisms): 1. Beta-adrenergic receptor stimulation 2. Impede antigen-antibody-mediated enzyme production and the release of histamine from leukocytes	Myocardial depression Arrhythmias Intrapulmonary shunting Cerebral vasodilation

primary reason to rapidly escalate therapies including the need to initiate mechanical ventilation.

10.8.1.2 Intravenous Fluids

Children with severe asthma may have hypovolemia due to poor oral intake and increased insensible fluid losses. Fluid replacement with a goal of euvolemia should be undertaken. Appropriate volume expansion may be necessary in the peri-intubation period, but aggressive overhydration should be avoided due to the risk of transpulmonary edema. Potassium replacement may be required due to beta-agonist-induced hypokalemia.

10.8.1.3 Inhaled Beta-Agonists

In the United States, albuterol is the most commonly used selective beta-2 agonist. Stimulation of the beta-2 receptors on bronchial smooth muscle cells leads to bronchodilation by the adenosine 3′,5′-cyclic monophosphate (cAMP)-mediated pathway. When delivered by aerosol, its effectiveness is dictated by distal drug delivery to the bronchial smooth muscle cells. Therefore, albuterol delivery is dependent upon dose, spontaneous tidal volume, gas flow, device used to deliver the gas, and the child's respiratory effort. Even under ideal conditions, only a small percentage of drug reaches the target cells. Therefore, dosing must be titrated accordingly. While the use of serial, fixed-dose, inhaled beta-agonist treatments is appropriate for moderate exacerbation, multiple studies support the use of continuous nebulization in severe cases. Continuous beta-agonist therapy is well tolerated by most patients and is less labor-intensive, thereby leading to a degree of cost-effectiveness when compared to many intermittent treatments.

Albuterol is an equal mixture of stereoisomers, (R)-albuterol, and (S)-albuterol. (R)-albuterol (also known as levalbuterol) is a therapeutically active component and selectively binds beta-2 receptors resulting in airway smooth muscle relaxation. Previously thought to be an inert enantiomer, in vitro studies now show that (S)-albuterol activates eosinophils, increases intracellular calcium in ASM cells enhancing airway hyperresponsiveness, and increases immune cell proliferation and cytokine production. The (S) enantiomer persists longer in plasma and lung tissue than the (R) enantiomer which results in accumulation of the (S) enantiomer with repeated dosing of albuterol.

Inhaled beta-agonists are the mainstay of therapy for the child with severe asthma.

Studies of (R)-albuterol in the severe pediatric asthma remain limited. The use of levalbuterol as an alternative to albuterol is not strongly supported by the literature. A randomized, double-blind trial in 2009 found no benefit in substituting high-dose continuous levalbuterol for albuterol and did not reduce the time on continuous therapy in children aged 6–18 years old. A 2012 meta-analysis of seven trials evaluating levalbuterol and albuterol for acute asthma in all age groups found that levalbuterol was not superior to albuterol in regard to respiratory rate, oxygen saturation, percentage change in FEV1, clinical asthma score, heart rate, side effects, and duration of ED care outcomes.

10.8.1.4 Inhaled Anticholinergic Agents

Ipratropium bromide is often used in combination with beta-agonists in severe asthma. Ipratropium exhibits bronchodilator effects through inhibiting parasympathetic-mediated bronchoconstriction and has the advantage of less cardiac toxicity than beta-agonists. Unlike the parasympatholytic atropine, ipratropium bromide does not impede mucociliary function. Although the evidence supporting the routine use of ipratropium has not been compelling, its relative safety can justify its use as an adjunct in severe asthma exacerbations. Clinicians should be aware of the potential for concomitant pupillary dilation (unilateral or bilateral) if the inhaled anticholinergic agent inadvertently contacts the eye.

10.8.1.5 Corticosteroids

Corticosteroids are required therapy in severe asthma due to their potent anti-inflammatory effects. In addition, corticosteroids may decrease mucous production and potentiate the effect of beta-agonists by upregulating beta-receptors. Children with severe asthma should receive their first dose of steroids upon presentation as the anti-inflammatory effect may be delayed up to 6 h.

Although oral corticosteroids are appropriate for most children presenting with severe asthma, children requiring PICU admission often require intravenous administration. Delayed gastric absorption, intestinal dysmotility, and/or vomiting can reduce the bioavailability of orally administered corticosteroids. There are several intravenous corticosteroid preparations available. Methylprednisolone is commonly used; however, dexamethasone and hydrocortisone are acceptable alternatives.

Intravenous corticosteroids should be administered as soon as possible to a child with severe asthma.

The adverse effects of short-term corticosteroid therapy include hyperglycemia, gastritis, sodium and water retention, hypertension, and increased susceptibility to infection. Muscle weakness and myopathy are possible, especially if a neuromuscular blocking agent is used concomitantly in children who require mechanically ventilation. If long-term therapy is required for children with asthma, suppression of the hypothalamic-pituitary-adrenal axis, demineralization of bones, myopathy, and growth failure may occur. Tapering of corticosteroid should be considered if the duration of systemic corticosteroid use is >2 weeks.

10.8.2 Second-Tier Therapies

10.8.2.1 Magnesium

Magnesium is an intracellular cation that is a key cofactor for cellular homeostasis. Inhibiting calcium intake into the smooth muscle cell prevents smooth muscle contraction and promotes bronchodilation. Magnesium reduces histamine and prostaglandin release by inhibiting mast cell degranulation. In addition, magnesium decreases acetylcholine release at motor nerve endings, which results in decreased muscle fiber excitability and bronchoconstriction.

Magnesium has been shown to produce a bronchodilator effect in a dose-dependent manner in children with mild to severe asthma. Studies have found that use of intravenous magnesium decreased hospital admission rate, reduced the need for mechanical ventilation, reduced hospital length of stay, improved short-term lung function, and reduced clinical symptom scores. Intravenous dosing of 25–50 mg/kg given over 30 min is the most common method of administering magnesium for severe asthma. Higher doses or rapidly infused magnesium may cause vasodilatation with resultant hypotension, and, therefore, close hemodynamic monitoring is required. Some authors have suggested the use of continuous infusions of magnesium for patients who are responsive to initial bolus dosing. Infusion rates of 15–25 mg/kg/h (not exceeding 2 g/h) have been safely used; however, infusions lasting greater than 4 h have not been formally evaluated. With repeated dosing or infusions, studies have suggested targeting serum magnesium levels to 4 mg/dL.

Inhaled magnesium has been evaluated in several large studies with mixed results. Nebulized magnesium appears to be safe, but it is unclear whether inhaled magnesium provides any clinical advantage over intravenous administration.

Potential side effects of magnesium administration include hypotension, flushing, arrhythmia, weakness, and CNS depression.

10.8.2.2 Helium/Oxygen Mixture

Helium is a biologically inert gas without inherent bronchodilatory or anti-inflammatory properties. Its use in the therapy of severe asthma is directly related to its physical properties that produce favorable gas flow characteristics. Normally, gas flow in the lung periphery is laminar because the large cross-sectional area of the distal bronchioles allows for slow, streamlined flow. In

contrast, upper airway flow is turbulent resulting in a high velocity and chaotic flow pattern. Although the diameter of the upper airway is far greater than an individual bronchial, the total cross-sectional area available for flow is far less in the upper airway.

In small airway disease, heliox is predicted to be much less effective because of the large cross-sectional area of the smaller airways. However, the pathophysiologic changes that asthma produces in the lower airway (edema, constriction, and mucous plugging) result in a reduction in the cross-sectional area available for flow. It is postulated that the favorable effects of heliox on gas flow reduce the pressure gradient that is required to achieve a given flow rate.

Turbulent flow can be predicted based upon the Reynolds number (Re) of a gas. Flow is turbulent when the $Re > 2500$. The formula for the Reynolds number is

$$Re = VD\rho$$

where V is gas velocity, D is the diameter of the airway, ρ is gas density, and μ is gas viscosity. Since helium possesses a lower gas density (approximately seven to eight times less dense than air), it results in a lower Reynolds number and, thus, reduces the likelihood of turbulent gas flow through narrowed airways. The conversion of turbulent to laminar flow allows distal gas delivery with a lesser pressure gradient and reduced velocity. Clinically, this results in improvement in gas exchange and a reduction in the work of breathing. In addition, helium/oxygen mixtures may inherently improve ventilation as carbon dioxide diffuses at a four times faster rate when compared to an oxygen/nitrogen mixture.

The potentially advantageous effects and the high safety profile of helium/oxygen mixtures have led its incorporation into acute asthma treatments. The most beneficial mixture (i.e., the lowest Reynolds number) is a mixture of 80% helium and 20% oxygen. Persistent hypoxia may lead to the need to increase the oxygen concentration to 30%. Utilizing mixtures with lower than 70% helium may compromise the ability to reduce turbulent flow.

Using a helium/oxygen mixture as a vehicle to deliver aerosolized beta-agonists may increase distal bronchial delivery and hasten the resolution of bronchospasm. A large systematic review of heliox-driven nebulized beta-agonist therapy showed an increase in peak expiratory flows and a reduction in hospital admissions, with a trend toward greater benefit in patients with severe exacerbations. Caution should be taken when heliox is delivered to a mechanically ventilated child. The mixture may cause erroneous flow and pressure measurements from most conventional ventilators, which are calibrated with only oxygen/nitrogen mixtures.

Helium/oxygen mixtures have a lower Reynolds number, leading to less turbulence through narrowed airways.

10.8.2.3 Intravenous Beta-Agonists

Theoretically, intravenous rather than aerosolized beta-agonists may be a superior method of drug delivery if bronchial constriction is so severe that aerosolized drug is prevented from reaching the distal airways. Intravenous beta-agonists such as terbutaline or salbutamol have been utilized to obtain beta-agonist bronchodilation via the systemic route. A loading dose of terbutaline 2–10 mcg/kg IV can be started prior to initial infusion rates of 0.1–0.4 mcg/kg/min. The infusion may be titrated by 0.2–0.4 mcg/kg/min every 30 min based on clinical response and adverse drug reactions. These parenteral agents are also more likely than inhaled albuterol to produce beta-agonist-induced adverse effects such as tachycardia, tremor, hypokalemia, and rarely cardiac ischemia.

Despite the paucity of evidence to support the routine use of intravenous beta-agonists, their use can be considered in children who are unresponsive to

increasing doses of inhaled bronchodilators. Limited data suggests these parenteral beta-agonists agents may decrease the need for intubation or shorten the course of mechanical ventilation for severe asthma. However, due to the potential for cardiac side effects, intravenous beta-agonists should be utilized only in children without concomitant heart disease.

10.8.2.4 Methylxanthines

Medications known as methylxanthines, most notably theophylline and aminophylline, have been long known to be potent bronchodilators. They are nonselective inhibitors of phosphodiesterase (PDE), including type 4, which is expressed in bronchial smooth muscle. Intracellular cAMP is metabolized to AMP by the PDEs. By inhibiting PDE, the intracellular concentration of cAMP increases which causes a decrease in phospholipase C-induced smooth muscle contraction. PDE inhibition is also thought to downregulate the inflammatory burst from pulmonary inflammatory cells. In addition, methylxanthines inhibit adenosine-induced bronchoconstriction, increase diaphragmatic contractility, stimulate endogenous catecholamine release, and promote diuresis and inhibition of afferent neuronal activity. Most notable is all these effects are mediated through pathways that are not beta-receptor dependent.

Despite multiple favorable mechanisms of action and a long history of use in asthma, methylxanthines are considered second-line therapy for acute exacerbations. Methylxanthines have been found to improve clinical asthma scores and airflow during acute exacerbations but have not consistently been shown to reduce PICU or hospital length of stay. Their narrow therapeutic window, and significant adverse effect profile (nausea, vomiting, agitation, tachycardia, decrease seizure threshold), has limited their use. Drug concentrations can also increase or decrease due to multiple interactions with medications that interact with the hepatic cytochrome P450 enzymes.

Methylxanthines may have a role in the treatment of some children with severe asthma, but they possess a small therapeutic window.

Clinicians should consider the use of methylxanthines in the beta-agonist refractory asthmatic while closely monitoring for the potential for drug toxicity. A 5–6 mg/kg loading intravenous dose of aminophylline over 20 min is needed to achieve a therapeutic concentration. Each 1.2 mg/kg dose raises the serum theophylline concentration by approximately 2 mg/L. Serum drug concentrations should be checked approximately 6 h after completing the loading dose and prior to starting an infusion. Serum target levels should be between 12 and 15 mcg/mL. After the loading dose is given, the recommended continuous aminophylline infusion rate is dependent upon the patient's age since methylxanthine drug clearance is decreased in neonates and infants. Clinician should be aware that methylxanthine clearance can be decreased in patients with pulmonary edema, congestive heart failure, hepatic disease, hypothyroidism, and sepsis with multiorgan failure.

10.8.2.5 High-Flow Nasal Cannula

High-flow nasal cannula (HFNC) is a device that allows the delivery of humidified oxygen via of supraphysiologic flow rates. Its use as noninvasive respiratory support for a variety of pulmonary disorders has increased dramatically. Current applications include neonatal respiratory distress, bronchiolitis, and pneumonia.

Mechanisms of action include dead space washout, reducing metabolic expenditure and providing some degree of positive pressure. By delivering gas at high inspiratory flow rates, nasopharyngeal dead space is replaced with warmed and humidified oxygen. This reduces both carbon dioxide rebreathing and the inspiratory work of breathing. Providing the airways with humidified and heated gas reduces the metabolic energy that would otherwise be expended to produce this gas conditioning. The amount of positive pressure provided

to distal airways is highly variable with a maximal end-expiratory pressure of 6–8 cm H_2O. The airway pressure is determined by the flow rate but also by how much flow leakage occurs at prong-nostril interface and from an open mouth. Flow rates range from 1 to 2 L/kg/min with maximal flow rates of 6 L/min in infants and 30 L/min in older children.

Complications related to HFNC are rare. Air leak syndromes including pneumothorax and pneumomediastinum have been reported in small infants and are likely related to higher than predicted delivery of distal airway positive pressure.

The favorable mechanisms of action and safety profile make HFNC an attractive modality for respiratory support in the child with moderate to severe asthma. Case reports and several observational studies suggest the HFNC is safe and effective in pediatric asthma. Further studies are required to determine its overall efficacy in the treatment of moderate to severe pediatric asthma.

10.8.2.6 Noninvasive Ventilation

Noninvasive ventilation (NIV) provides positive pressure, either synchronized with negative pressure breaths (spontaneous) or with a set backup rate (timed). Positive pressure is delivered via tight fitting facial or nasal mask. The set pressure can be either continuous positive airway pressure (CPAP) or bi-level inspiratory and expiratory airway pressures (BiPAP). This mode of ventilation is frequently used as an early intervention in children with impending hypoxic respiratory failure and may have a safe role in moderate to severe asthma exacerbations.

NIV positive pressure can reduce airway resistance by stenting distal airways, thereby increasing distal beta-2 agonist delivery. In addition, NIV can reduce respiratory muscle work, improve atelectasis, and promote collateral ventilation. The use of this mode of respiratory support requires patient cooperation and may require mild to moderate sedation in some children. Other limitations include an inability to clear oral secretions and a potential to increase gastric distention and risk of aspiration.

NIV may be considered in children with moderate to severe asthma not responsive to first-tier therapies (e.g., continuous bronchodilators). However, current evidence is not conclusive in determining if NIV reduces rates of endotracheal intubation or shortens length of stay in children with moderate to severe asthma.

10.8.3 Third-Tier Therapies

10.8.3.1 Ketamine

Ketamine is a sedative-hypnotic that has been used extensively to facilitate intubation in asthmatic children. Its current use has been expanded to provide sedation in both the pre-intubation and post-intubation period. The increasing preference to use ketamine as a sedative for children with moderate and severe asthma has been due to its potential to provide some degree of bronchodilation.

Ketamine produces bronchodilation by several proposed mechanisms of action. These include (1) potentiating endogenous catecholamine release, thereby further stimulating beta-2 adrenergic receptors, (2) inhibition of vagal pathways producing anticholinergic effects on bronchial smooth muscle, (3) inhibition of NMDA receptor-induced bronchoconstriction, (4) reversal of histamine-induced bronchoconstriction, and (5) downregulation of inducible nitric oxide synthetase in pulmonary tissue.

Ketamine has notable adverse effects which include hallucinations, bronchorrhea, laryngospasm, tachycardia, hypertension, and lowering seizure

threshold. Use of anti-sialagogues (atropine or glycopyrrolate) may be required if to reduce airway secretions.

Due to the sedative and bronchodilatory effects of ketamine, it is the preferred medication to facilitate intubation in the asthmatic child with impending respiratory failure.

Ketamine should be the sedative of choice to facilitate endotracheal intubation. Low-dose ketamine may play a role in avoiding mechanical ventilation and facilitating NIV in the child with severe asthma. Due to a paucity of high-quality data, ketamine infusions should be used with caution as a sedative in a spontaneous breathing or mechanically ventilated asthmatic children. Further studies are warranted to determine the efficacy of ketamine in pediatric patients with severe asthma.

10.8.3.2 Inhaled Anesthetics

A child with a refractory exacerbation and progressive hypoxemia despite maximal therapy and mechanical ventilation warrants a trial of inhalational anesthetic agents as a rescue maneuver. Halothane, isoflurane, and sevoflurane have all been found to have bronchodilatory effects which are thought to be due to beta-adrenergic receptor stimulation, reduction of vagal tone, and decreasing histamine release. Halothane has both significant negative inotropic and arrhythmogenic properties and should be avoided. Operationally, anesthetic delivery may be difficult. Anesthesia machines often do not have the capacity to ventilate the severe asthmatic for prolonged periods. A standard ICU ventilator can be fitted to deliver anesthesia, but ongoing delivery requires the presence of an anesthesiologist at the bedside.

10.8.3.3 Extracorporeal Membrane Oxygenation (ECMO)

In severe refractory respiratory failure secondary to asthma, ECMO remains a viable rescue option. The institution of ECMO may allow time for therapeutics (bronchodilators, glucocorticoids) to take effect. Once on ECMO support, pulmonary hygiene and lung rest can be facilitated while avoiding ventilator-induced lung injury. ECMO requires a multidisciplinary team not only proficient in managing the circuit but also capable of addressing the multiorgan derangements that can occur during mechanical cardiopulmonary support. Small case series have reported success utilizing ECMO. Further data is required to determine the optimal timing of ECMO relative to increasing support on mechanical ventilation.

10.9 Mechanical Ventilation for Severe Asthma in Children

The goal of mechanical ventilation during asthma is to provide adequate oxygenation and ventilation and allowing respiratory muscles to rest.

Most children who are treated promptly and aggressively for severe asthma will improve and not progress to respiratory failure requiring mechanical ventilation. However, a rare subset of children may have progressive or rapid respiratory deterioration that requires endotracheal intubation and mechanical ventilation. These patients represent a clinical challenge, both in the decision and process of endotracheal intubation and in the strategies utilized to provide ongoing ventilatory support. The goal of mechanical ventilation of the child with severe asthma is to provide adequate oxygenation and ventilation until the airway obstruction subsides and to allow respiratory muscles to rest by assuming the work of breathing.

Preparation is paramount during intubation, as most morbidity and mortality of childhood asthma occur during or shortly after endotracheal intubation.

Indications for the initiation of mechanical ventilation in severe asthma include respiratory or cardiac arrest, refractory hypoxemia, or a rapidly worsening sensorium. The presence of a respiratory acidosis should not be the sole prompt for intubation. However, rapidly rising carbon dioxide in the setting of obvious fatigue and/or progressive hypoxia is a clear indication for intubation. There are relative indications for endotracheal intubation, in which the deci-

sion must be made in the context of disease progression and therapy refractoriness. Relative indications include a rapidly increasing pulsus paradoxus, the loss of the ability to speak, and increasing serum lactate levels.

Once the decision is made to intubate, careful preparation is essential. A significant portion of morbidity and mortality due to severe asthma occurs in the peri-intubation period. Due to the predictable hemodynamic response to the initiation of positive pressure and the likelihood of concomitant volume depletion, appropriate fluid resuscitation should commence prior to intubation. Ketamine with a benzodiazepine is an effective combination to provide sedation. Use of atropine or glycopyrrolate should be considered to decrease bronchorrhea due to asthma or secondary to ketamine. Propofol is an acceptable alternative sedative if hypotension is not present. Neuromuscular blockade can be achieved with the use of a rapidly acting nondepolarizing paralytic such as rocuronium. Due to the potential side effects of histamine release and hyperkalemia, succinylcholine is generally avoided, especially in infants. Opioid agonists such as morphine can worsen bronchospasm secondary to a release of histamine and should be avoided. Fentanyl causes less histamine release and may be considered if analgesia is required.

Mechanical ventilation of the severe asthmatic can be challenging due to rapid changes in airflow dynamics during ventilation. The asthmatic may experience acute airway plugging from copious secretions and severe bronchoconstriction during agitation or may develop a pneumothorax secondary to air trapping. A pneumothorax should be considered with any acute hemodynamic or respiratory deterioration.

Multiple ventilatory modes have successfully supported children with respiratory failure due to asthma. No consensus exists in terms of what is the optimal mode of ventilation. Synchronized intermittent mandatory ventilation (SIMV) delivered with either pressure control (SIMV/PC) or volume control (SIMV/VC) are common choices. Pressure-regulated volume control (PRVC) uses a decelerating flow rate and combines elements of pressure and volume ventilation. PRVC guarantees a set tidal volume to be delivered with the lowest peak pressure possible to minimize barotrauma.

Mechanical ventilator settings should be adjusted to provide a physiologically acceptable level of oxygenation and ventilation while avoiding excessive airway pressure and dynamic lung hyperinflation. General guidelines on initial settings include an initial tidal volume set at approximately 6–10 mL/kg to maintain an inspiratory plateau pressure of <30 cm H_2O, a ventilation rate between 6 and 14 breaths/min depending on the age of the patient, a relatively short inspiratory time that allows a prolonged inspiratory to expiratory ratio (1:4 or higher depending on the rate), and possibly the application low positive end-expiratory pressure (PEEP) while monitoring auto-PEEP closely. Initial oxygen concentration is set at 100% and weaned as tolerated.

Adjusting the respiratory rate is best done with careful attention to the physical exam and exhalation flow pattern. The clinician should auscultate breath sounds and visualize chest excursion after multiple breaths. Full exhalation should occur prior to commencement of the next breath. If not, residual volume from each breath will lead to breath stacking, hyperinflation, and an increased risk of pneumothorax and hemodynamic compromise (Fig. 10.7).

If the exhaled flow is not completed, then either the mechanical respiratory rate must be decreased or the expiratory time must be increased. However, to obtain minute ventilation enough for carbon dioxide removal, higher tidal volumes and peak inspiratory pressures may need to be tolerated. Normal carbon dioxide levels are not necessary and indeed may lead to preventable barotrauma. Clinicians should allow "permissive hypercapnia" to limit

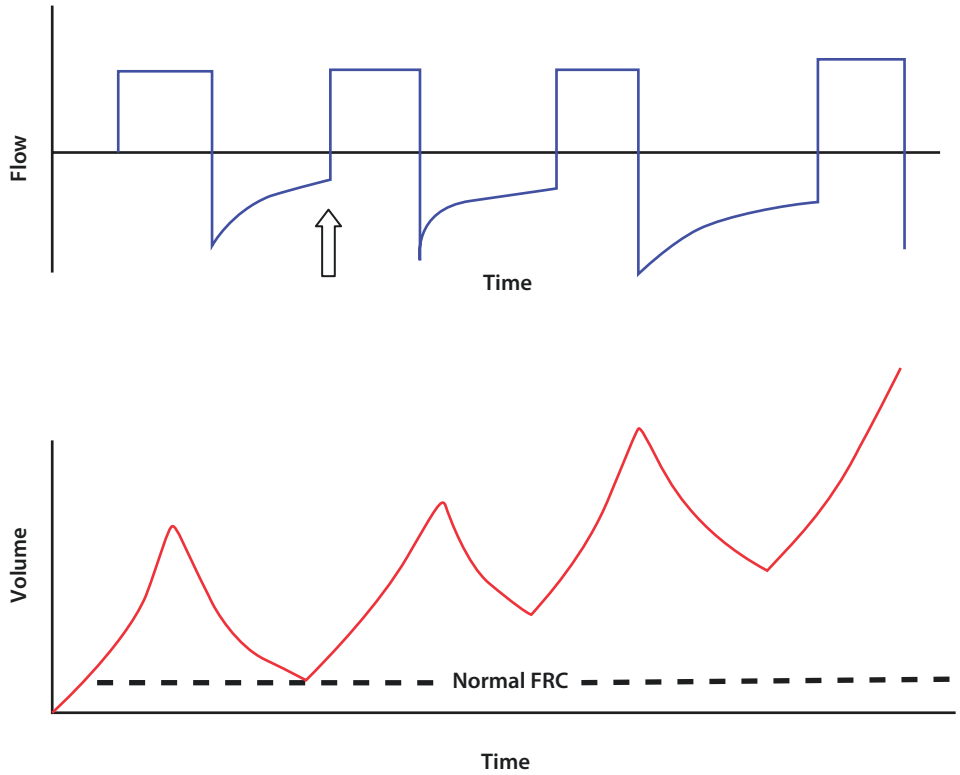

Fig. 10.7 Progressive dynamic hyperinflation in the setting of severe expiratory airflow obstruction. Inspiration begins prior to completion of exhalation (arrow) as seen on flow versus time graph. Air trapping above FRC ensues, as seen on the volume versus time graph

ventilator-induced lung injury. $PaCO_2$ levels as high as 90 mmHg may need to be tolerated during the early phases of mechanical ventilation.

10.10 Monitoring During Mechanical Ventilation

Although mechanical ventilation may be lifesaving in the asthmatic with respiratory failure, multiple challenges can occur after the institution of positive pressure. Monitoring changes in airway dynamics during the mechanical ventilation of a child with severe asthma is essential. Serial measurements of peak inspiratory pressures (PIP) and plateau pressures and monitoring for the development of progressive hyperinflation enable the clinician to respond to dynamic airway changes that are common during mechanical ventilation for asthma.

Peak inspiratory pressure often is used as a proxy for distal alveolar pressure. However, elevated airway resistance causes the measurement of peak inspiratory pressure to be poorly reflective of peak alveolar pressure. Instead, measurement of both peak inspiratory pressure and plateau pressures provides a better assessment of changes in compliance and resistance in the mechanically ventilated asthmatic. These measurements can aid clinicians in rapid troubleshooting and in monitoring worsening or improving disease.

Dynamic compliance is derived from measuring the tidal volume in relation to the delta of the PIP and PEEP and is affected by gas flow.

$$\text{Dynamic compliance} = \text{tidal volume}$$

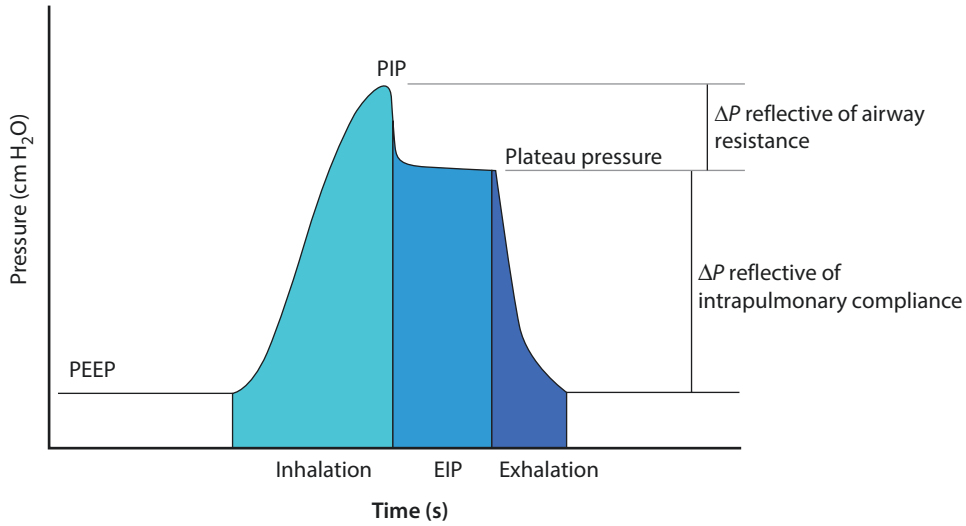

Fig. 10.8 Pressure during end inspiratory pause. Note the delta between the peak and plateau (*EIP* end inspiratory pause)

Static compliance utilizes plateau pressure in place of PIP. The plateau pressure is measured at the termination of inspiratory flow and therefore is unaffected by gas flow.

$$\text{Static compliance} = \text{tidal volume}$$

Because PIP is measured during ongoing gas flow, it may be reflective of both lung compliance and resistance to airflow in proximal and distal airways. To differentiate reduced compliance and increased resistance, a plateau pressure should be measured by instituting a 3 s flow pause at the end of inspiration (Fig. 10.8). An increasing PIP in the setting of an elevated plateau pressure reflects a reduction in dynamic compliance of the lung. This may be due to worsening parenchymal disease but may also be due to asynchrony, hyperinflation, or a pneumothorax. An increased PIP in the setting of a low plateau pressure (< 30 cm H_2O) reflects increased airway resistance.

Increased peak inspiratory pressure with little change in plateau pressure usually reflects increased airway resistance.

In summary, normally PIP is slightly greater than plateau pressure. Increasing PIP should prompt troubleshooting (Fig. 10.9). Concomitant elevations in PIP and plateau pressure are usually reflective of hyperinflation due to auto-PEEP or developing parenchymal disease. Increased PIP with little change in plateau pressure usually reflects increased airway resistance. It is not uncommon for peak inspiratory pressures to be much higher than plateau pressures during mechanical ventilation for asthma. An increased PIP-plateau pressure delta is reflective of increased airway resistance (bronchospasm, plugging). A decreasing PIP-plateau pressure delta can serve as useful marker for clinical improvement.

Auto-PEEP occurs if an insufficient expiratory time impedes full exhalation of alveolar and is reflective of air trapping.

Auto-PEEP can occur if insufficient expiratory time impedes full exhalation of alveolar gas. Auto-PEEP is reflective of air trapping and is not uncommon in mechanically ventilated asthmatic children. Auto-PEEP can be quantified by occluding the expiratory port of the ventilator at end expiration. The proximal airway pressure will equilibrate with alveolar pressure and permit measurement of auto-PEEP. Of note, auto-PEEP measured by the end-expiratory occlusion maneuver can have inconsistent results and requires paralysis as expiratory muscle contraction can cause artificial elevation. Auto-PEEP can underestimate the severity of hyperinflation if there is poor communication between the distal alveoli and the proximal airways. This can occur if pre-

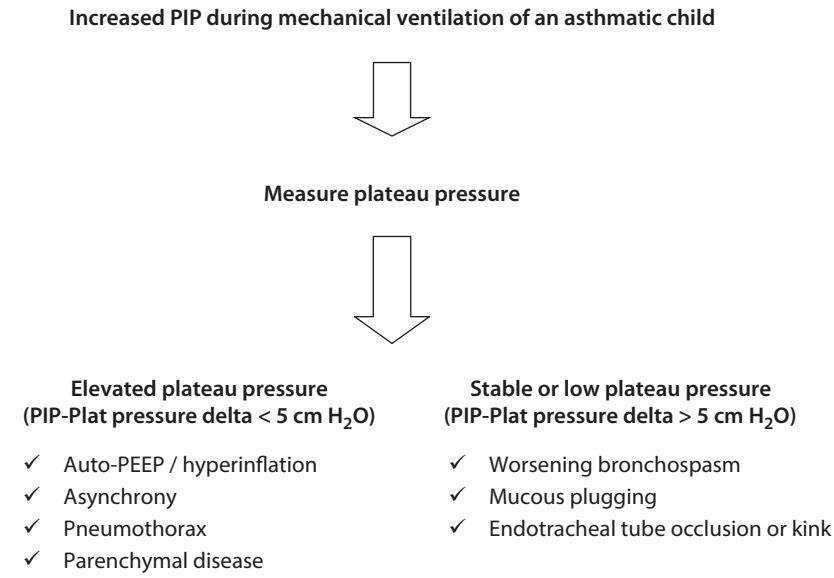

Fig. 10.9 Algorithm for evaluation of increasing PIP during mechanical ventilation

mature airway closure occurs prior to end expiration. Therefore, elevations in plateau pressures may be a more reliable and practical method to monitor lung hyperinflation.

Although counterintuitive, the application of extrinsic PEEP may provide some benefit during positive pressure ventilation of the asthmatic. Extrinsic PEEP (usually about 80% of the baseline auto-PEEP) can improve inspiratory muscle effectiveness. Use of low levels of extrinsic PEEP in mechanically ventilated children with spontaneous breaths may decrease the inspiratory work of breathing by stenting open airways and decreasing the pressure gradient required to overcome auto-PEEP. Therefore, when selecting a PEEP setting, the intrinsic auto-PEEP must be carefully considered. The extrinsically applied PEEP should always be lower than the auto-PEEP. Adding excessive PEEP may result in overinflation, air leak, and hemodynamic compromise from increased intrathoracic pressure.

The airway obstruction that occurs in severe asthma can be detected and monitored by several flow waveforms. A flow-volume loop (Fig. 10.10) can demonstrate increased airway resistance causing a decrease in maximum expiratory flow. This results in a concave shape to the expiratory limb on the flow-volume loop.

End tidal carbon dioxide tracings may also display evidence of expiratory obstruction and prolongation. There will be a delayed upstroke prior to reaching the peak expired carbon dioxide level transforming the waveform into a "shark fin" appearance. Normally, a plateau is maintained after reaching the end tidal carbon dioxide value (Fig. 10.11).

10.11 Complications During Mechanical Ventilation of Asthma

Many complications can occur during the initiation and maintenance of mechanical ventilation in severe asthma. These complications include air leak due to positive pressure-induced barotrauma (pneumomediastinum, pneumo-

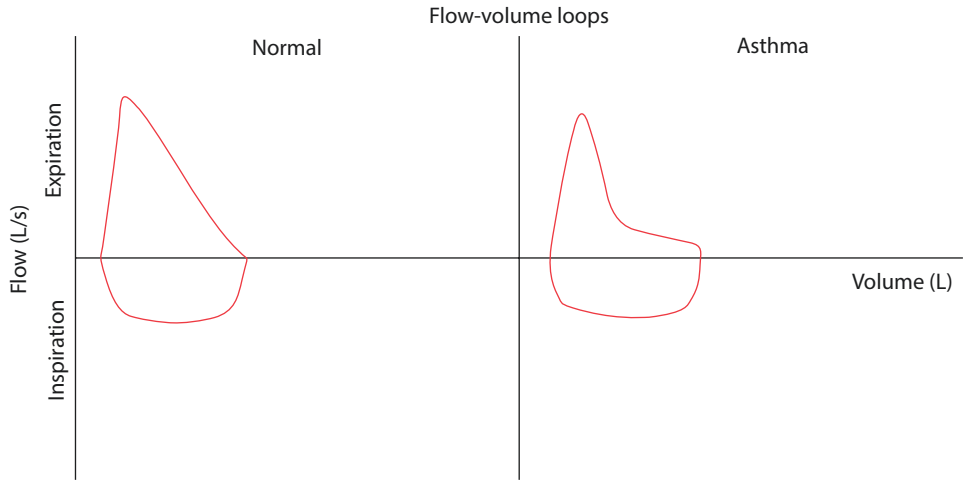

Fig. 10.10 Concave expiratory flow pattern seen with lower airway obstruction

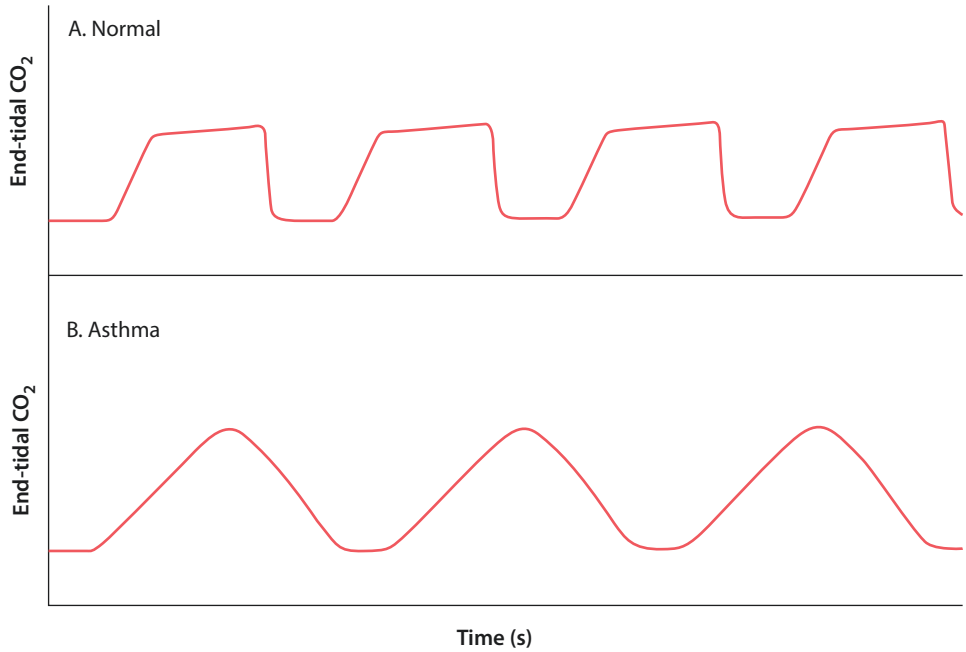

Fig. 10.11 **a** Normal capnograph revealing normal early expiratory upstroke followed by alveolar plateau phase. **b** Capnograph during bronchospasm revealing prolonged expiratory phase, poor plateau, and elevated end tidal CO_2 level

thorax, subcutaneous emphysema), nosocomial tracheitis and pneumonia, and mucus plugging and atelectasis. Complications such as pneumothorax and hemodynamic compromise can be limited if plateau pressures are maintained less than 30–35 cm H_2O and auto-PEEP is less than 15 cm H_2O. Marked hemodynamic compromise can occur and has been discussed in detail above. Prolonged weakness may occur in children ventilated for severe asthma. The risk of myopathy appears to increase with the concomitant use of steroids and neuromuscular blocking agents. The etiology of this myopathy is not completely understood but may be related to a loss of protein synthesis or altered electrical excitability of muscle fibers. Weakness may be protracted and require inpatient physical rehabilitation after PICU discharge.

Review Questions

1. Which of the following statements regarding the epidemiology of childhood asthma is correct?
   A. A child with asthma has a high likelihood of requiring intubation and mechanical ventilation if hospitalization is required for his/her care.
   B. Although the prevalence of pediatric asthma has increased, the associated mortality has sharply decreased due to improved critical care services.
   C. The "hygiene hypothesis" which suggests that the early exposure to microbial infections results in asthma has become accepted as the sole explanation for the increased prevalence of asthma.
   D. The phenotype of asthma is likely the result of a complex interaction between environmental factors and a single gene mutation.
   E. Prevalence of childhood asthma has increased, and average annual prevalence is higher in children <18 years of age as compared to adults.

2. A 14-year-old girl is admitted to the PICU for status asthmaticus. It is her third admission in 5 years, each occurring in late fall. Her parents inquire about potential triggers and how best to avoid them. Which statement is appropriate to include in your response?
   A. Exacerbations often have unidentifiable triggers.
   B. Exacerbations often have triggers that cannot be modified.
   C. Exacerbations in adolescent females are often misdiagnosed. An evaluation for vocal cord dysfunction is required.
   D. Environmental irritants including second-hand smoke may predispose children with bronchial hypersensitivity to severe asthma exacerbations.
   E. Viral infection is a common trigger for exacerbation but usually only in infants.

3. Poiseuille's equation is used to explain the laminar flow rate of an incompressible fluid down a column. Which component of this equation best explains why children are at greater risk for airway obstruction than adults?
   A. The airway radius
   B. The density of gas
   C. The distance of the airways
   D. The laminar flow of air
   E. The pressure gradient from the trachea to the alveolus

4. Which statement is true regarding the underlying pathophysiology of asthma?
   A. Asymptomatic asthmatic children may have low-grade persistent inflammation.
   B. Neutrophils play a major role in mediating inflammation and releasing of leukotrienes and histamine.
   C. Mucin production is increased due to goblet cells hyperplasia, but the composition of mucin remains unchanged.
   D. The fractional excretion of nitric oxide decreased due to the inflammatory response seen in asthma.
   E. Remodeling leads to increased airway smooth muscle mass but does not contribute to airway hyperresponsiveness and hypersensitivity.

5. An important component of the pathophysiologic cardiopulmonary interactions that can lead to decreased cardiac output during severe asthma exacerbation is:
   A. Right ventricular preload increase
   B. Right ventricular afterload decreases due to hyperinflation

C. Increased left ventricular afterload due to greater transthoracic pressure gradient
D. Increased left ventricular preload
E. Overall myocardial ischemia due to inadequate oxygenation

6. A 4-year-old male is admitted to the pediatric intensive care unit with respiratory distress secondary to an acute exacerbation of asthma. He was started on albuterol as a continuous nebulized solution of 15 mg/h in the ED but was unable to tolerate oral prednisone. He is awake and speaks in short sentences. His oxygen saturation is 92% on 40% face mask oxygen, and he has normal inspiratory sounds. He has marked expiratory wheezing with maximal accessory muscle use. Considering these clinical findings, it would be *most* important to initiate which of the following medications?
A. IV azithromycin
B. Nebulized ipratropium
C. IV magnesium
D. IV solumedrol
E. IV theophylline

7. A 9-year-old male is transferred to the pediatric intensive care unit with respiratory distress secondary to an acute exacerbation of asthma. He has marked expiratory wheezing with maximal accessory muscle use. Despite aggressive therapy consisting of intravenous steroids, continuous β-agonist aerosol therapy, and anticholinergic aerosols, the child continues to deteriorate and requires intubation. Which of the following induction medications for the intubation would be *most* appropriate?
A. Etomidate
B. Fentanyl
C. Ketamine
D. Propofol
E. Thiopental

8. A 13-year-old male with severe status asthmaticus was evaluated in the emergency department and admitted to the PICU. His initial arterial blood gas data is pH 7.23, PCO2 58, PO2 79 on room air. In the ED, he was started on NC 4 lpm, received nebulized albuterol × 3, and IV methylprednisolone. He continues to have inspiratory and expiratory wheezes with decreased air entry. You recommend starting nebulized ipratropium with the next dose of albuterol. Of the following, which best explains the mechanism by which nebulized ipratropium may be of benefit in this patient?
A. Inhibition of calcium intake into smooth muscle cell of the airway
B. Increase of intracellular cyclic guanosine monophosphate
C. Blockage of nicotinic receptors
D. Antagonism of airway leukotriene receptors
E. Blockade of muscarinic acetylcholine receptors

9. A 14-year-old male with bicuspid aortic valve stenosis is admitted to PICU with his first asthma exacerbation. His response to continuous albuterol, ipratropium bromide, and steroids is minimal. Terbutaline is started at 1 mcg/kg/min and increased to 4 mcg/kg/min with some improved response. During the increased titration, the pulse pressure starts to widen along with increasing tachycardia. The patient then goes into cardiac arrest after complaining of back and chest pain. The *most* likely explanation for his cardiac arrest is
A. Acute asphyxial asthma
B. Impaired cardiac filling
C. Aortic dissection

D. Severe hypokalemia
E. Myocardial ischemia

10. On day 2 of mechanical ventilation of an asthmatic child, the respiratory therapist reports a sudden increase in peak inspiratory pressure from 19 to 29 cm H_2O. You perform an inspiratory hold to measure the plateau pressure. The plateau pressure is 18 cm H_2O. What is the most likely explanation for elevated PIP?
A. Parenchymal disease
B. Auto-PEEP
C. Pneumothorax
D. Asynchrony
E. Mucous plugging

11. Which of the following medications used in the treatment of status asthmaticus exerts its effect by inhibiting the inward movement of calcium into smooth muscle, thereby preventing further bronchoconstriction?
A. Albuterol
B. Aminophylline
C. Helium
D. Ipratropium
E. Magnesium

12. Which of the following medications used in the treatment of status asthmaticus exerts its effect via a combination of inhibition of phosphodiesterase and adenosine-induced bronchoconstriction?
A. Albuterol
B. Aminophylline
C. Helium
D. Ipratropium
E. Magnesium

13. A 16-year-old female with status asthmaticus has failed to respond to first-tier therapies when admitted to the PICU. The pediatric intensivist decides to start a helium/oxygen mixture of 80% helium/20% oxygen. Which of the following characteristics *best* describes the mechanism of action for helium/oxygen mixtures in this setting?
A. Increased Reynolds number, creating conditions that favor laminar flow
B. Decreased Reynolds number, creating conditions that favor laminar flow
C. Less viscous than oxygen/nitrogen mixtures
D. Higher mass density than oxygen/nitrogen mixtures
E. Less gas velocity than oxygen/nitrogen mixtures

14. A 12-year-old male with a known history of refractory asthma is transferred to the pediatric intensive care unit (PICU) with a severe exacerbation. He is placed on a non-rebreather oxygen mask because his oxygen saturation ranges 84–89%. He is promptly started on intravenous solumedrol, continuous inhaled albuterol, and intermittent ipratropium bromide. A few hours into his admission, his respiratory distress persists. Intravenous magnesium and an aminophylline infusion are added to his therapeutic regimen. His vital signs reveal a temperature of 37.8 °C, heart rate of 152 bpm, respiratory rate of 36 breaths/min, and a blood pressure of 125/82 mmHg. His air exchange is fair with expiratory wheezing and marked retractions. He has bounding pulses. The nurse reports that he has anisocoria with his right pupil 7 mm and his left 4 mm. He answers questions appropriately in two-word sentences. Which of the following is the *most* appropriate course of action?

A. Perform a thorough neurologic exam, and if reassuring, continue his current care with frequent monitoring of his neurologic exam and serum drug levels.
B. Perform a thorough neurologic exam, and if reassuring, decrease the dose of albuterol as its high-dose effect may be resulting in a tachycardia that is potentially compromising CNS perfusion.
C. Perform a more thorough neurologic exam, and if reassuring, obtain an EEG as aminophylline may be associated with subclinical seizures.
D. Prepare for immediate intubation using neuroprotective strategies.
E. Perform a more thorough neurologic exam, and if reassuring, order a stat head computerized axial tomogram.

15. A 7-year-old male with a severe asthma exacerbation has a rapidly deteriorating level of consciousness. An arterial blood gas reveals a pH 7.26, $PaCO_2$ 56 mmHg, and PaO_2 52 mmHg. Pulse oximetry reveals saturations persistently below 85%. A decision is made to urgently intubate the child. The child receives ketamine (1 mg/kg), glycopyrrolate, and rocuronium (0.9 mg/kg) to facilitate the intubation. The child is intubated on the first attempt with end tidal carbon dioxide confirmation. While taping the endotracheal tube, he becomes profoundly hypotensive with significant respiratory variation in his arterial pressure waveform. He has decreased air entry in all lung fields. Which of the following most likely represents the primary pathophysiology of the hypotension?
A. A tension pneumothorax secondary to the initiation of positive pressure
B. Decreased cardiac output due to myocardial ischemia
C. Decreased cardiac output secondary to ketamine effect
D. Inaccurate zeroing of the arterial catheter pressure transducer as the bed was raised to facilitate intubation of the child
E. Relative intravascular volume depletion secondary to increased insensible losses, decreased oral intake, and increased intrathoracic pressure

16. A 9-year-old, 30 kg young girl with an acute exacerbation of severe asthma has required intubation and mechanical ventilation. She is placed in a pressure-regulated volume control mode with the following ventilator settings:
- IMV rate: 24 breaths/min
- Peak end-expiratory pressure (PEEP): 5 cm H_2O
- Tidal volume: 300 mL
- I-time: 1.0 s
- Fraction of inspired oxygen: 0.40

In addition, she has an auto-PEEP of 5 cm H_2O, a peak inspiratory pressure of 42 cm H_2O, a plateau pressure of 34 cm H_2O, and an end-expiratory flow of 3 L/min. Her most recent arterial blood gas reveals:
- pH: 7.34
- $PaCO_2$: 49 mmHg
- PaO_2: 72 mmHg

Which of the following is an appropriate ventilator adjustment?
A. Increase the I-time
B. Increase the PEEP
C. Increase the tidal volume
D. Decrease the respiratory rate
E. Increase the fraction of inspired oxygen

Answers

1. E
2. D
3. A
4. A
5. C
6. D
7. C
8. E
9. E
10. E
11. E
12. B
13. B
14. A
15. E
16. D

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Pediatric Acute Respiratory Distress Syndrome

Garrett Keim and Nadir Yehya

Contents

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Learning Objectives

- Define pediatric acute respiratory distress syndrome (PARDS).
- Understand how the alveolar-endothelial barrier maximizes gas exchange while minimizing fluid flux.
- Understand the mechanisms for the pulmonary edema seen in PARDS.
- Describe the important biochemical events that mediate inflammatory lung injury seen in PARDS.
- Identify how changes in compliance and functional residual capacity lead to intrapulmonary shunting and hypoxemia seen in PARDS.
- Recognize the distinct temporal pathologic changes in PARDS necessitating specific targeted therapies.
- Describe how the "open-lung model" maximizes oxygen exchange while minimizing ventilator-induced lung injury.
- Understand the roles for prone positioning, HFOV, APRV, corticosteroids, surfactant, and nitric oxide in the treatment of PARDS.

11.1 Introduction

Clinicians have long known the severe pulmonary complications that can accompany life-threatening illness or injury. In 1967, Ashbaugh and colleagues described what has now become known as the acute respiratory distress syndrome (ARDS). Their initial description of the syndrome in civilian patients was further appreciated in victims of nonthoracic trauma during the Vietnam War. ARDS has been known by other terms: Da Nang lung, shock lung, noncardiogenic pulmonary edema, and wet lung. Comparison was made with neonatal respiratory distress syndrome, acquired surfactant deficiency was postulated, and management with mechanical ventilation was described. ARDS was subsequently reported in pediatric patients, and the term "acute respiratory distress syndrome" came to be used in place of "adult respiratory distress syndrome." We describe here the epidemiology, pathogenesis, and management of pediatric ARDS (PARDS). As much of the evidence comes from adult ARDS, we liberally reference adult data and make specific references to pediatric considerations when appropriate.

In 1994, the European-American Consensus Conference formalized the first widely accepted definition for both acute lung injury and ARDS: acute onset of bilateral infiltrates on chest radiograph, no clinical evidence of left atrial hypertension or wedge pressure <18 mmHg, and a $PaO_2/FiO_2 \leq 300$ for acute lung injury and ≤200 for ARDS. The definition was refined and updated in 2012 with the publication of the Berlin ARDS definition. Berlin ARDS is divided into mild, moderate, and severe based on PaO_2/FiO_2 (eliminating the confusing "acute lung injury/non-ARDS" category) and removes the need for documenting a wedge pressure given the declining incidence of pulmonary artery catheterization. In neither 1994 nor 2012 were pediatric considerations addressed in the definitions of ARDS.

11.1.1 PALICC Definition of PARDS

In 2015, the Pediatric Acute Lung Injury Consensus Conference (PALICC) group published the first pediatric specific consensus definition of PARDS (Table 11.1). PALICC utilizes the more commonly used (in pediatrics) metrics of oxygenation index (OI) and oxygenation saturation index (OSI) to define

Table 11.1 Comparison of PALICC PARDS and Berlin ARDS

Characteristic	PALICC PARDS	Berlin ARDS
Oxygenation	*Mild*: 4 ≤ OI < 8 (5 ≤ OSI < 7.5) *Moderate*: 8 ≤ OI < 16 (7.5 ≤ OSI < 12.3) *Severe*: OI ≥ 16 (OSI ≥ 12.3)	*Mild*: 200 < P/F ≤ 300 mmHg (PEEP or CPAP ≥ 5 cm H_2O) *Moderate*: 100 < P/F ≤ 200 mmHg (PEEP ≥ 5 cm H_2O) *Severe*: P/F ≤ 100 mmHg (PEEP ≥ 5 cm H_2O)
Timing	Within 7 days of clinical insult	Within 1 week of clinical insult or worsening respiratory symptoms
Pulmonary edema	Judged not to be caused by cardiac failure or fluid overload	Not explained by cardiac failure or fluid overload; requires objective assessment such as echocardiography to exclude hydrostatic edema
Chest radiograph	New infiltrate(s) consistent with acute pulmonary parenchymal disease (can be unilateral)	Bilateral opacities not explained by effusion or lung collapse
Noninvasive ventilation criteria	Full-face bi-level positive pressure ventilation with CPAP ≥ 5 cm H_2O PF ≤ 300 SF ≤ 264	CPAP 5 ≥ cm H_2O only for mild ARDS

and stratify PARDS. Uses of OI (mean airway pressure (mPaw) × FiO_2 × 100/PaO_2) and OSI (mPaw × FiO_2 × 100/SpO_2) were considered more appropriate stratification variables due to the incorporation of mPaw rather than PaO_2/FiO_2, the preferred metric of hypoxemia in adult ARDS. PALICC also explicitly has alternative stratification using SpO_2 when PaO_2 is unavailable (i.e., OSI) and has less restrictive radiographic criteria (unilateral versus bilateral). Prospective validations of the PALICC definition have demonstrated good performance of these OI- and OSI-based severity categories for predicting mortality, suggesting good face validity.

11.1.2 Epidemiology

PARDS has a distinct epidemiology, including a lower mortality, than adult ARDS.

There are significant differences between the adult ARDS and PARDS epidemiology, risk factors, and mortality rates. Adult ARDS is comprised of patients with multiple medical comorbidities and has mortality rates reported between 27% and 45%. PARDS, on the other hand, has a lower mortality (18–27%). A history of prematurity, with its unique effects on physiology, is a comorbidity specific to children. Other important comorbidities in PARDS include congenital diseases, immunodeficiencies, hematologic malignancies, and bone marrow transplantation. As survival has improved in recent years, post-ARDS outcomes have been of growing interest. A follow-up study of a cohort of ARDS survivors demonstrated a 1-year mortality of 11%, as well as continued functional limitations and impaired quality of life out to 5 years post-ARDS. Survivors of ARDS have shown effects on ability to return to work out to 5 years and effects on psychological well-being. Post-PARDS outcomes are

much less understood. A single-center cohort study showed that 1-year mortality of PARDS survivors is 5.5%. More work is needed to better understand the post-ICU course for survivors of PARDS.

11.1.3 Etiology, Initiation, and Subtypes of PARDS

ARDS is a heterogeneous disease based on etiology, genetic predisposition, underlying mechanisms of disease, and response to therapy.

ARDS and PARDS are defined as clinical syndromes representing a heterogeneous disease based on etiology, genetic predisposition, and underlying mechanisms of disease. The varying etiologic events vary widely and are postulated to affect severity of disease and mortality. This has led to attempts to divide both ARDS and PARDS into broad categories that are more useful for prognostication and targeting future therapeutic interventions. Most commonly, these divisions have been between direct (pulmonary) versus indirect (non-pulmonary) etiologies, infectious versus noninfectious etiologies, and focal versus non-focal distribution (based on lung imaging). Direct lung injury is a result of damage at the level of the alveolar epithelium from conditions such as pneumonia, gastric aspiration, and drowning. Conversely, indirect lung injury is a result of systemic processes such as sepsis, burns, blood transfusion reactions, and non-pulmonary trauma that cause secondary lung injury by damage initially to the vascular endothelium. Recent publications looking at these different categories have shown unique clinical presentations of indirect and direct PARDS. Indirect PARDS is associated with a higher severity of illness, while direct PARDS has worse oxygenation. Despite these differences, no difference in mortality was seen between these two categories. Significant work is required to better understand and delineate how and which etiologic models are utilized in future PARDS trials.

Despite the fact that ARDS is a multifactorial, heterogeneous disease, there exists some degree of genetic predisposition to the development of ARDS. This predisposition is likely multigenic and, at present, there are multiple candidate genes that have demonstrated association with development of ARDS in adults. There are no studies to date in children investigating whether specific genes are implicated in the development of PARDS.

11.2 Anatomic and Physiologic Considerations in PARDS

Pulmonary interactions essential to the understanding of the pathogenesis and treatment of PARDS include:

- Starling's hypothesis
- Alveolar surface tension
- Lung compliance
- Functional residual capacity (FRC)
- Intrapulmonary shunt

11.2.1 Starling's Hypothesis and Lung Fluid in PARDS

Starling's forces: Capillary hydrostatic and colloid osmotic pressure determine fluid flux across the alveolar-endothelial barrier.

The lung's endothelial-alveolar barrier is a highly complex and efficient system, maximizing gas exchange and minimizing fluid flux (Fig. 11.1). The alveolar epithelium and capillary endothelium form a barrier in which fluid flux is determined by forces outlined in Starling's hypothesis. The force tending to push fluid *out* of the capillary and *into* the interstitium is the capillary hydro-

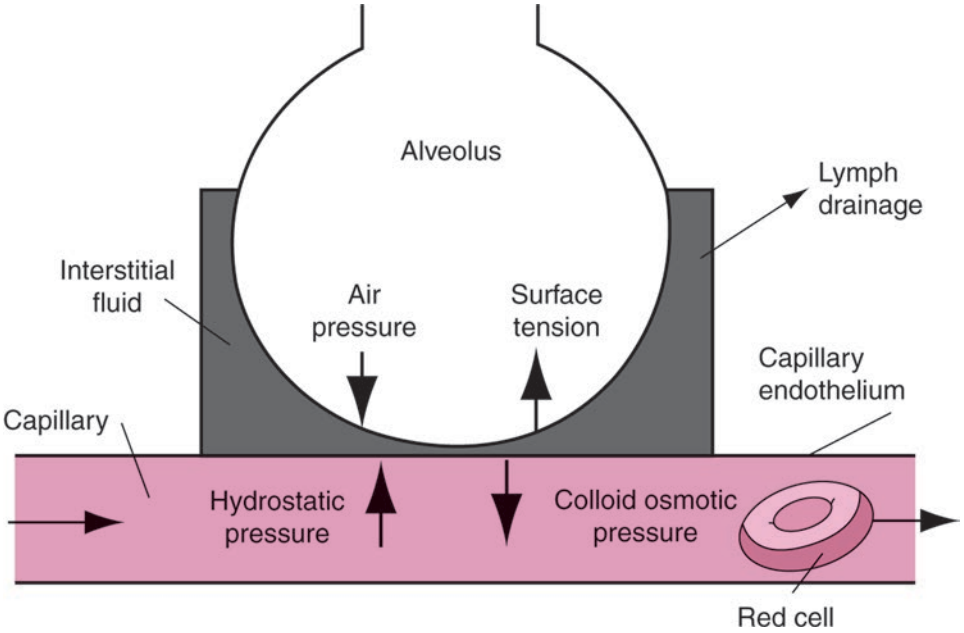

Fig. 11.1 Starling's forces determining fluid flux across the lung's endothelial-alveolar barrier. (From Rhoades and Tawner (1995))

static pressure minus the interstitial hydrostatic pressure ($P_c - P_i$). The force tending to pull fluid *into* the capillary is the capillary oncotic pressure minus the interstitial oncotic pressure ($\pi_c - \pi_i$). This net oncotic force also depends on the effectiveness of the capillary wall in preventing the flow of proteins, which is referred to as the reflection coefficient (σ). The relationship between the sum of these forces and fluid movement is the inherent permeability of the endothelium to water, and the surface area available for fluid flux also affects this relationship. The filtration coefficient accounts for these factors and is referred to as K. Thus:

$$\text{Fluid flow across capillary} = J_v = K\left[\left(P_c - P_i\right) - \sigma\left(\pi_c - \pi_i\right)\right]$$

Disruption of the alveolar-endothelial barrier leads to the accumulation of proteinaceous edema fluid in alveoli of the PARDS lung.

On balance, there is a net egress of fluid out of the capillary. Fluid pushed out of the capillary will be reabsorbed by perivascular lymphatics until the lymphatic capacity is overwhelmed, at which point alveolar fluid accumulates. The pulmonary edema associated with ARDS and PARDS is *not primarily* due to increased capillary hydrostatic pressure. It is "noncardiogenic" in nature. After an initial insult, a pro-inflammatory cascade is set in motion that ultimately compromises alveolar-endothelial integrity (disrupts the filtration coefficient K) and favors edema formation. As the barrier is now more permeable to larger proteins, there is an efflux of proteinaceous fluid into the interstitium, and if the alveolar epithelia are damaged, into the airspace. The plasma proteins in the edema fluid further contribute to lung injury by causing surfactant dysfunction with loss of surface tension. The protein-rich edema fluid that has been quantified in the alveoli of ARDS patients confirms that barrier disruption and loss of oncotic balance are initially responsible for edema formation. Increased capillary hydrostatic pressure may occur later due to hypoxic pulmonary vasoconstriction, microvascular thrombosis, and even subsequent cardiac dysfunction. Note that cardiac dysfunction can coexists with ARDS and PARDS but cannot be the primary driver of pulmonary edema. This is often difficult to differentiate in clinical practice and is a shortcoming of the syndromic definitions used.

11.2.2 Alveolar Surface Tension

A soap bubble serves as an excellent model to explain the physiologic force of surface tension. The spherical bubble has both outer and inner moist surfaces that are in direct contact with air. A bubble maintains its spherical shape because water molecules are more attracted to each other than to the surrounding air molecules. This creates surface tension, the inwardly directed force that reduces surface area while maintaining the integrity of the sphere. Pressure is maintained within the sphere to counter the natural forces favoring collapse. Laplace described these forces mathematically with the following equation:

$$P = 4T / R$$

P = pressure within the sphere, T = surface tension, R = radius.

When both inner and outer surfaces are in contact with air, the constant 4 is used; if only one surface is in contact with air, the constant 2 is used. The alveolus can be thought as an incomplete sphere where the moist inner surface is in contact with air and the moist outer surface is in contact with tissue. The Laplace relationship when applied to an alveolus is therefore:

$$P = 2T / R$$

Surfactant's ability to reduce surface tension is amplified as the size of the alveoli is decreased. This allows for equalization of pressures among interconnected alveoli of varying sizes. Without functional surfactant, alveoli are prone to collapse and fluid influx, leading to regional atelectasis and worsening pulmonary edema.

A problem arises when the principle is applied to interconnected alveoli with different dimensions. According to Laplace, the pressure in the smaller alveoli would exceed that of the larger alveoli (since it has a smaller radius, thus higher P), causing escape of air from the smaller unit into the larger unit. This would create an unstable lung with a propensity for smaller units to become atelectatic (Fig. 11.2). This would indeed be the case if the alveolus were coated with interstitial fluid instead of surfactant. Surfactant is secreted by type II pneumocytes and is made up of lipids (primarily dipalmitoyl phosphatidylcholine) and proteins that are spread over the inner surface of the alveoli. Surfactant dramatically reduces surface tension with its effects becoming greater as the diameter of the alveolus decreases (lower T as radius decreases). Surfactant's ability to stabilize surface tension allows equalization of pressure in large and small alveoli and thus prevents atelectasis. Surfactant also reduces the tendency of fluid to move from the tissue to the alveolus. Without surfac-

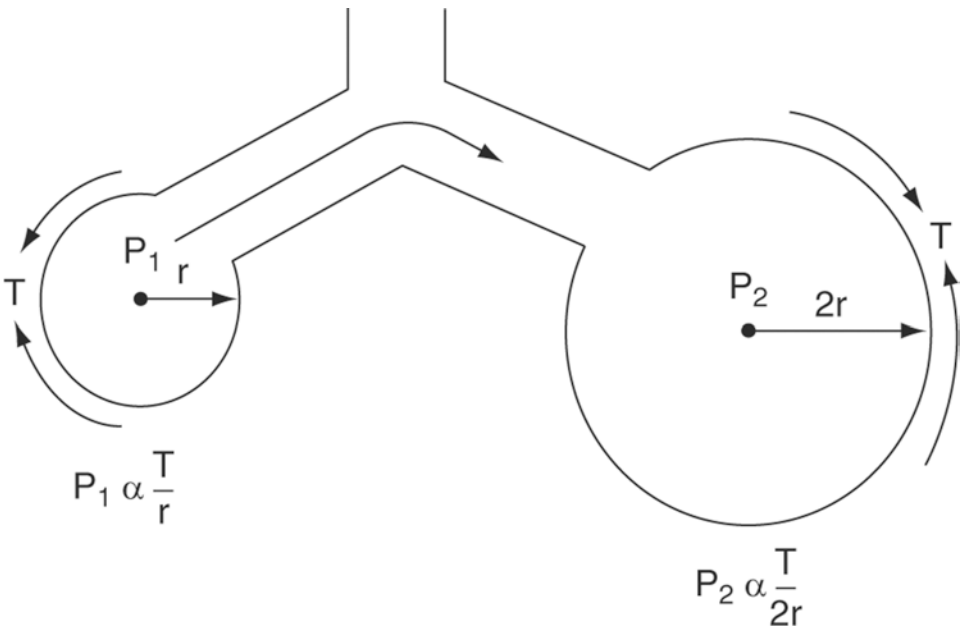

Fig. 11.2 According to Laplace's law, the pressure in the smaller alveolus exceeds the larger one causing air to empty into the larger alveolus with subsequent collapse of the smaller alveolus. This is not the case because the lung is lined with surfactant, and the alveoli are structurally linked to each other. Surfactant's ability to reduce surface tension is amplified as the diameter of the alveoli is decreased. This allows for equalization of pressures among interconnected alveoli of varying sizes

tant, surface tension forces would be greater at a given pressure causing fluid to be drawn into the alveolus. In effect, surfactant preserves the intra-alveolar pressure available to resist fluid influx into the alveolus.

Surfactant's ability to reduce surface tension is greatly compromised by the protein-rich edema fluid that accumulates in the alveoli of the ARDS lung. This results in both alveolar collapse and further edema formation. Macroscopically, this leads to dramatic changes in lung mechanics. Of particular importance are the reductions in lung compliance and functional residual capacity.

Without functional surfactant, alveoli are prone to collapse and fluid influx, leading to regional atelectasis and worsening pulmonary edema.

11.2.3 Compliance

The volume change per unit pressure change is known as the compliance of a system.

$$\Delta V / \Delta P$$

Lung compliance can be measured by calculating the slope of the pressure-volume curve. The pressure-volume curve of ARDS lungs is less steep than a healthy lung, indicating that a greater change in pressure is needed to produce the same change in volume (Fig. 11.3). ARDS lungs are functionally smaller and less compliant and are often referred to as being "small and stiff." Accompanying this reduction in compliance is a dramatic fall in the functional residual volume of the lung.

The ARDS lung requires a far greater change in pressure to produce the same incremental change in lung volume as a healthy lung.

Elastance is the reciprocal of compliance and is defined mathematically as $\Delta P/\Delta V$. It is the tendency of a hollow structure (i.e., lung) that is under pres-

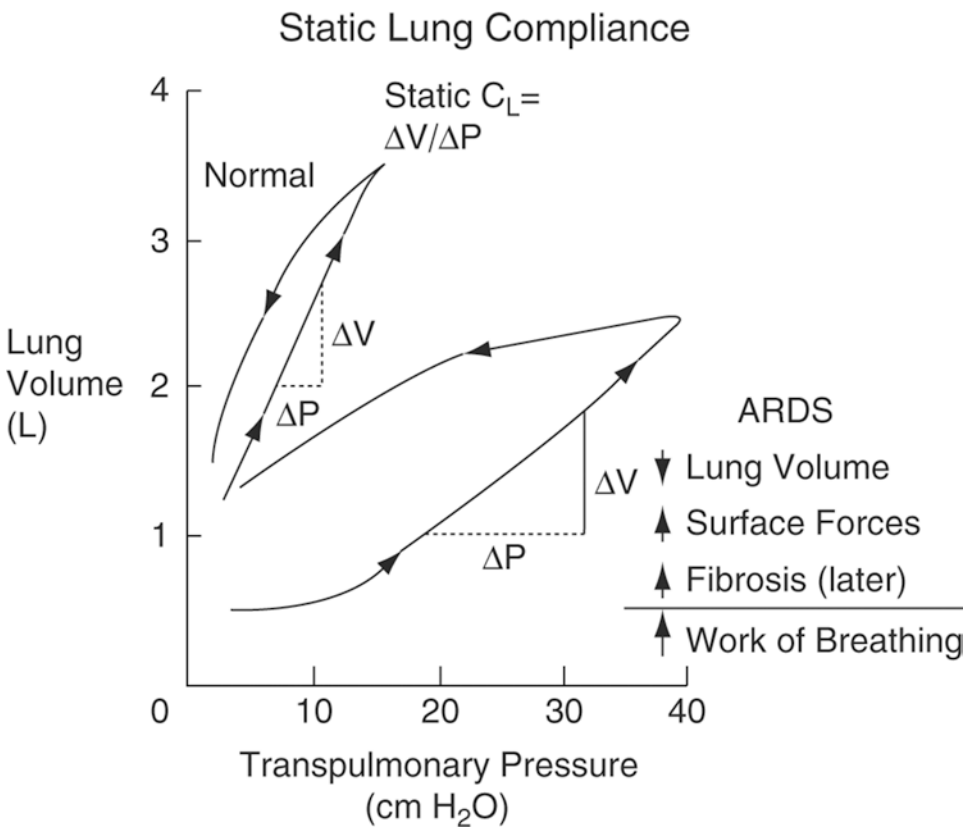

Fig. 11.3 Change in pressure-volume curve due to multifactorial pathology causing decreased lung compliance. The ARDS lung requires a far greater change in pressure to produce the same incremental change in lung volume as a healthy lung

sure to recoil to its original dimensions upon removal of the distending pressure. The lung, chest wall, and total respiratory system have individual compliance and elastance properties. The compliance-elastance relationship can be simplified as compliance determines the inspiratory pressure required to distend the lung, and its reciprocal elastance determines the expiratory volume the lung will return to when the distending pressure is removed.

Distinctive differences in pulmonary biomechanics, specifically elastance, have been described between PARDS resulting from direct lung injury and PARDS from indirect lung injury. Studies have found that the elastance of the *lung* is higher in direct lung injury as compared to indirect (non-pulmonary) PARDS. Conversely, the elastance of the *chest wall* was more than twofold higher in indirect PARDS than in direct lung injury, likely because the generalized inflammatory process causing edema formation in the lung is also occurring in the skin, muscle, and fat layers of the chest wall. The high elastance of the chest wall is consistent with a stiffer and noncompliant chest wall. The increased elastance of the chest wall in indirect PARDS may be also related to increased intra-abdominal pressure, which is seen commonly in patients with indirect PARDS.

11.2.4 Functional Residual Capacity (FRC)

FRC is the volume of the lung at which the inherent forces of the chest wall to maintain expansion balance the lung's inherent tendency to collapse. FRC is greatly reduced in the child with PARDS due to alveolar collapse and edema.

FRC is the volume of gas that remains in the lung after normal expiration. It is at this volume that the inherent forces of the chest wall to maintain the expanded shape of the thorax balance the lung's inherent tendency to collapse. FRC is reduced in PARDS due to alveolar filling with edema fluid and alveolar collapse secondary to surfactant destruction/dysfunction. Although upon gross inspection the postmortem lung of a child with PARDS is large and edematous, physiologically, the lung is operating at a reduced FRC and thus is functionally small. In adult ARDS, this is referred to as the "baby lung": the concept that the functionally available lung in ARDS is reduced to a much smaller volume. This reduction in FRC results in a diminished surface area available for gas exchange and is associated with hypoxemia. Recruitment of these nonfunctional alveolar units by mechanical ventilatory strategies that open lung and attempt to regain a normal FRC improves gas exchange largely due to restoring surface area and decreasing intrapulmonary shunting.

11.2.5 Intrapulmonary Shunting in PARDS

When considering ventilation-perfusion (V/Q) relationships, it is useful to appreciate the extremes of V/Q mismatching (◘ Fig. 11.4). Dead space ventilation represents one extreme; an alveolus receives ventilation without perfusion. The V/Q ratio approaches infinity in such cases. Large conducting airways exemplify normal anatomic dead space. The other extreme, intrapulmonary shunt (IPS), exists when the alveolar unit is unventilated but remains perfused (V/Q → 0). This "intrapulmonary shunt" blood returns to the left side of heart without the benefits of gas exchange and thus appears as mixed venous blood. A small anatomic shunt exists in the normal state (approximately 3% of blood returning to the left heart). This is made up of blood returning from the bronchial circulation (thebesian veins) and coronary venous blood draining directly into the left ventricle. This normal anatomic shunt partially accounts for the fact that the partial pressure of arterial O_2 is slightly less than the partial pressure of alveolar O_2.

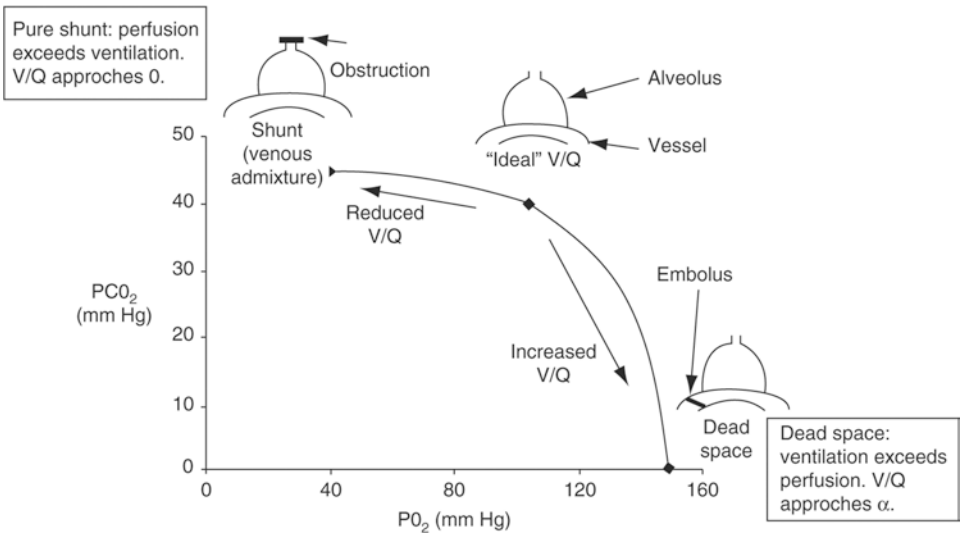

Fig. 11.4 Ventilation-perfusion relationships including extremes: pure shunt and dead space

An important distinction between a true right to left intrapulmonary shunt (IPS) and hypoxemia due to V/Q mismatching (low V/Q ratio but not 0) is the response to 100% FiO_2. There is no increase in PaO_2 with the administration of 100% FiO_2 in a complete IPS, whereas a modest increase in PaO_2 will occur if a low V/Q is the cause of hypoxemia. This relationship is complicated by the possibility of converting low V/Q units to a true IPS due to absorption atelectasis after the administration of 100% FiO_2. Due to the heterogeneous nature of the lung injury associated with ARDS, both IPS and low V/Q units contribute to hypoxemia. However, evidence suggests that IPS is responsible for a larger portion of the hypoxemia. Pathologically, completely atelectatic and fluid-filled alveoli act to produce this IPS. Clinically, this is reflected by little to no improvements in PaO_2 despite the administration of 100% FiO_2 to children with severe PARDS. Therefore, therapies directed at recruitment of alveolar units participating in IPS are more useful in reversing hypoxemia than the administration of high FiO_2 alone.

Normal V/Q relationships in healthy subjects dictate that the majority of ventilation is directed to dependent areas of the lung due to diaphragmatic activity, where fortuitously (by gravitational effects) perfusion is greatest. In the PARDS lung, most of the disease occurs in dependent areas. This leads to poorly aerated dependent sections that continue to be perfused, thus leading to greater V/Q mismatch. This is exacerbated by ventilating subjects in the supine position, where the weight of abdominal contents causes crowding of dependent lung regions. Reduced diaphragmatic activity from sedation and paralysis and dependent atelectasis from edematous lung anteriorly worsen this existing V/Q mismatch by reducing dependent ventilation. Recently, the sponge model has been used to describe why dependent areas tend to have the greater degree of alveolar deaeration. The lung sponge model theory suggests that the increased edema that accumulates down the anterior to posterior axis of the lung leads to superimposed pressure on dependent areas. This superimposed pressure along the gravitational axis causes dependent areas to become deaerated to a greater degree than nondependent counterparts. In this model, the edema is believed to be predominantly in the interstitium causing alveolar collapse by compression, whereas in the air-fluid interface model (alveolar barrier injury), the edema is predominantly in the alveoli. Regardless, in both models, the compromised alveoli are unavailable for gas exchange and FRC is decreased.

Atelectatic and fluid-filled alveoli create low V/Q segments leading to degrees of intrapulmonary shunting and hypoxia.

11.3 Inflammatory Mediators in PARDS

Regardless of the etiology of PARDS, inflammatory mediators are involved in tissue damage as well as lung repair. We will highlight a few inflammatory markers implicated in PARDS.

Pro- and anti-inflammatory mediators are implicated in PARDS pathogenesis.

Tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) are considered the main mediators of early inflammation. Both are released by activated macrophages and lead to an activation of secondary inflammatory mediators including cytokines, reactive oxygen species, and adhesion molecules. Interleukin-6 (IL-6) is produced by macrophages, endothelial cells, and fibroblasts in response to endotoxin, TNF-α, or IL-1β. IL-6 induces pyrexia, and the concentration of this acute-phase protein has been demonstrated to be a predictor of adult ARDS severity. Interleukin-10 (IL-10) serves as an anti-inflammatory cytokine and has been shown to attenuate the production of pro-inflammatory cytokines by alveolar macrophages during ARDS. Patients with ARDS have been shown to have lower concentrations of IL-10 (bronchoalveolar lavage fluid and circulating levels) than those who are at risk for ARDS but do not develop the disease. Transforming growth factor-β (TGF-β) is a pro-inflammatory cytokine that serves as a mediator of tissue fibrosis. The role of TGF-β is likely important in the fibroproliferative phase.

Granulocyte macrophage-colony stimulating factor (GM-CSF) serves a key role in the host defense response in the lung and is necessary for the function of alveolar macrophages. GM-CSF has attracted attention as a therapeutic agent for subjects at risk for ARDS and PARDS. A small randomized clinical trial of GM-CSF infusion in adults showed no improvement in mortality or ventilator-free days. Intercellular adhesion molecule-1 (ICAM-1) is an endothelial surface protein that is upregulated during inflammation. ICAM-1 deficiency impedes neutrophil recruitment. Increased ICAM-1 expression has been demonstrated in a variety of pro-inflammatory conditions and is also a future therapeutic target in ARDS.

11.4 Pathologic Phases of PARDS

Traditionally, three distinct time-dependent histopathological phases of ARDS have been described in adults (Fig. 11.5). While these phases and time course have not been corroborated in PARDS, we present them here as a framework for understanding the progression of the underlying disease process.

11.4.1 Acute Exudative Phase

The initial phase of ARDS typically lasts 1 week and is characterized by:

- Capillary-alveolar barrier injury (damage to type I pneumocytes)
- Development of protein-rich noncardiogenic pulmonary edema
- Surfactant dysfunction and deficiency due to damage to type II pneumocytes
- Neutrophil activation and alveolar infiltration with the initiation of inflammatory cascades
- Pulmonary hypertension
- Beginning of hyaline membrane formation

Distinct time-dependent histopathological phases described in adult ARDS are the acute exudative phase, subacute proliferative phase, and fibrosis with or without recovery.

These events result in pulmonary edema, reduced FRC, and impaired gas diffusion with resultant V/Q mismatching, and intrapulmonary shunting. This leads to profound hypoxemia. It is not uncommon for the patient to have systemic inflammatory response syndrome (SIRS) during this phase, either from the ARDS itself or from the underlying etiological trigger (i.e., sepsis).

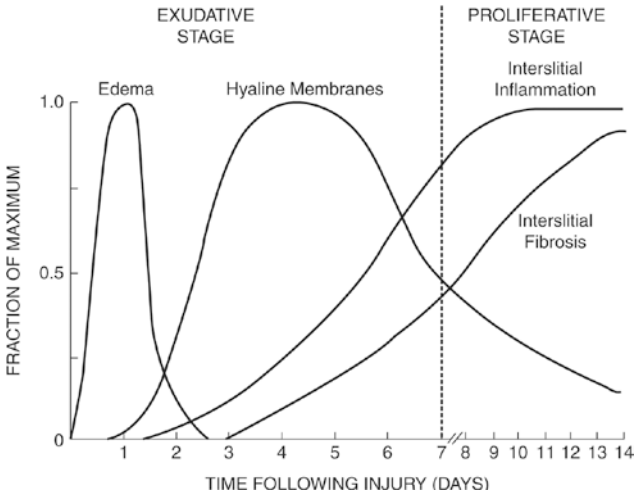

Fig. 11.5 Acute respiratory distress syndrome time course. Fibrotic phase with or without recovery follows the acute exudative and proliferative stages

11.4.2 Subacute Proliferative Phase

The subacute phase begins 7–10 days after insult and is characterized by:

- Fibroblast proliferation
- Ongoing inflammation
- Hyperplasia of type II pneumocytes
- Widening of alveolar septa due to cellular proliferation and organization of hyaline membrane
- Worsening pulmonary hypertension

Modest improvement in oxygenation is seen with the application of PEEP, but ventilation may become impaired due to increasing dead space. Inflammatory mediators indicative of SIRS may decrease during this phase.

11.4.3 Fibrosis With or Without Recovery

From 1 to 3 weeks, the lungs may develop fibrosis and remodeling. It is important to note that not all patients progress through all stages, and some may show resolution in the exudative phase. Also, those progressing to fibrosis may have variable long-term lung function. The long-term sequelae of PARDS remain largely unknown. Adult follow-up studies have shown worsened exercise tolerance and quality of life in ARDS survivors. One retrospective cohort study of survivors of PARDS showed functional status scale score changes consistent with new morbidity in 23% of survivors. More work is needed to better understand the long-term effects of PARDS on children's lives. Biomarkers of fibroproliferation, such as type III procollagen, have received great interest as they may identify a subset of subjects who may benefit from systemic corticosteroids to limit fibrosis.

11.5 Management

Care of the child with PARDS is complex, involving not only mechanical ventilation strategies to address the severe hypoxemia while limiting ventilator-induced lung injury (VILI) but also supportive care with regard to fluid balance, sedation and potential paralysis, treatment of etiologic agent and comorbidities, and modulators of oxygen delivery. We will highlight management strategies as well as consensus recommendations where they exist.

11.5.1 Ventilatory Management: *Maximize PEEP, Minimize VILI*

The main principles of adult ARDS management, extrapolated to PARDS, are limiting damaging distension and opening the lung using PEEP.

Studies have identified a reduction in mortality in adults with ARDS when using a protective lung strategy. This approach advocates for minimizing VILI via restricting tidal volumes to 6 mL/kg for patients and lower for those with excessive plateau pressures (>30 cm H_2O). These strategies have not been validated in PARDS although are commonly adopted and will be discussed with greater detail in the coming sections. A separate but related strategy emphasizes maintenance of FRC using recruitment maneuvers and positive end-expiratory pressures (PEEP), the "open-lung" approach. This approach also emphasizes reduction of VILI, primarily by invocation of the damaging effects of atelectasis rather than by reduction of alveolar stretch per se. As with tidal volume and peak/plateau pressure reduction, these approaches have not been validated in PARDS.

11.5.1.1 Optimizing PEEP

PEEP aids in the recruitment of collapsed alveoli and redistribution of alveolar fluid into the interstitial space. PEEP also decreases the shear forces on the alveoli produced by the repetitive opening and closing of alveoli during mechanical ventilation.

The maintenance of PEEP during mechanical ventilation has several theoretical benefits. PEEP aids in the recruitment of collapsed alveoli and the redistribution of alveolar fluid into the interstitium, thereby improving oxygenation. PEEP leads to the maintenance of functional residual capacity (FRC), thereby decreasing the shear forces on the alveoli that are produced by repetitive opening and closing during mechanical ventilation. Overall, PEEP improves the overall compliance of the lung by increasing and maintaining the FRC to a steeper point on the pressure-volume curve (Fig. 11.6) and homogenizing the distribution of gas in the lung. In a volume mode of ventilation with constant flow characteristics, movement to a more advantageous position on the pressure-volume curve will result in a smaller increase in peak and plateau pressure than the applied increase in PEEP. However, if alveolar overdistention predominates, increases in PEEP will result in an increase in peak and plateau pressures equal to or greater than the applied incremental increase in PEEP. Similarly, in a pressure mode of ventilation, incremental increases in PEEP will result in augmentation of tidal volume as alveolar recruitment occurs (increased compliance). When one reaches the flatter portion of the pressure-volume curve, an incremental increase in PEEP will fail to further increase tidal volume.

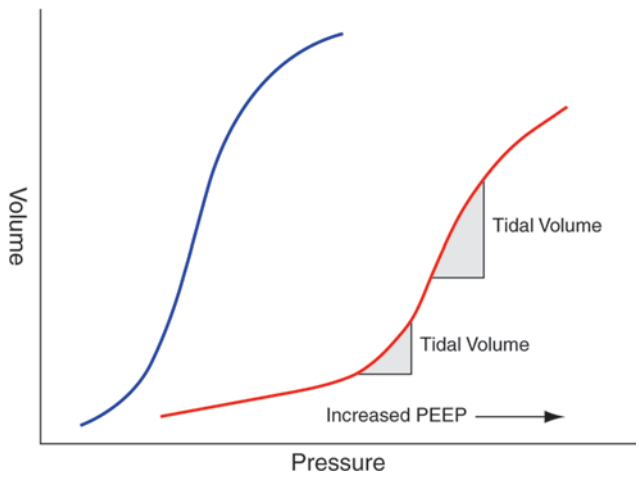

Fig. 11.6 Normal and ARDS pressure-volume curves. The application of PEEP in the noncompliant ARDS lung allows a shift to a more favorable position on the pressure-volume curve

PEEP can have detrimental effects including overdistention of compliant alveoli and the reduction of venous return to the right heart. There are multiple ways to set PEEP. One can identify the lower inflection point of the pressure-volume curve (where collapsed alveoli are opened) using modified super-syringe techniques in modern ventilators (◘ Fig. 11.6). The PEEP level is then initiated above this point to maintain alveolar recruitment. Alternatively, one can incrementally increase PEEP and monitor changes in peak and plateau pressures (when in volume control) or tidal volume (when in pressure control). ARDSNet has set forth a protocolized PEEP/FiO_2 titration strategy for adult ARDS, increasing PEEP to lower FiO_2 requirement. No comparable table exists specifically for PARDS, but the use of the ARDSNet table may be useful in PARDS PEEP titration. A retrospective analysis of multiple PARDS datasets demonstrated an independent association with mortality for patients managed with a PEEP lower than recommended by ARDSNet protocol after controlling for recorded potential confounders. In light of this, it is reasonable to consider ARDSNet guidelines during PEEP titration for PARDS. More work in this area is needed, although it generally appears that PARDS is managed by lower PEEP than would be recommended by adult ARDS guidelines.

The judicious application of PEEP improves the overall compliance of the lung by increasing the FRC to a steeper point of the pressure-volume curve.

It should be noted that in four adult ARDS trials of high versus low PEEP, no survival advantage was seen with higher PEEP. In the most recent trial, which was coupled with aggressive recruitment maneuvers prior to setting high PEEP, the high PEEP group demonstrated higher mortality, although this may have reflected problems with the recruitment and PEEP protocol rather than with high PEEP per se.

11.5.1.2 Minimizing VILI

The application of positive pressure ventilation can produce further inflammatory changes in the lung. To reduce the possibility of worsening VILI, a judicious approach to mechanical ventilation is required. Several strategies can be employed to reduce VILI. The use of PEEP helps to improve oxygenation via maintenance of FRC, decreasing the shear forces on alveoli by preventing repetitive collapse and reopening (atelectrauma). Oxygen toxicity is reduced by limiting FiO_2, usually to a goal of <60%. The optimal use of PEEP allows appropriate weaning of FiO_2. Limitation of volutrauma, lung injury due to overdistension of alveoli, and barotrauma, alveolar injury due to exposure to high pressures, are addressed using small goal tidal volumes and limiting peak and plateau pressures. Permissive hypercapnia to an arterial pH target of 7.25 is often employed to help limit VILI and is usually well tolerated. This rarely may require the addition of sodium bicarbonate or another buffer. The first positive trial in adult ARDS demonstrated the superiority of tidal volumes of 6 mL/kg versus 12 mL/kg, and limiting plateau pressures to 30 cm H_2O rather than 50. The relationship between tidal volumes, pressures, and outcomes is less clear in PARDS, although peak pressures have consistently been associated with poor outcomes. PALICC recommends keeping tidal volumes <8 mL/kg and limiting peak and plateau pressures in the absence of direct trial evidence.

Reduction of tidal volumes and limiting peak and plateau pressures are central to lung-protective ventilation strategies to limit VILI.

11.5.1.3 High-Frequency Oscillatory Ventilation (HFOV)

When considering the mechanical forces contributing to VILI, the use of HFOV in the treatment of ARDS has obvious theoretical advantages. HFOV provides the extreme in the open-lung, low tidal volume approach. Oxygenation is achieved by maintaining lung volume at a sustained mPaw. The mPaw is usually set 4–8 cm H_2O above the mPaw on conventional mechanical ventilation (CMV). Ventilation occurs as small tidal volumes (1–2 mL/kg; sub-dead space)

that are delivered at high frequencies (8–15 Hz or 480–900 breaths/min) around the set mPaw. The major disadvantages of HFOV include the need for heavier sedation, often paralysis, and the reduced pulmonary toilet due to concerns about derecruitment with suctioning.

HFOV and APRV are consistent with the open-lung approaches to maximize alveolar recruitment. Their use should be cautiously considered in PARDS patients failing conventional ventilation.

Two simultaneously published large randomized control trials in adults with moderate to severe ARDS have called the use of HFOV into question. The OSCAR study showed no statistically significant effect on 30-day mortality between HFOV and CMV. The OSCILLATE study was stopped after indication of higher relative risk of hospital mortality in patients receiving HFOV, although this may be related to the specific HFOV protocol used. Large randomized controlled trials of the use of HFOV in modern PARDS are lacking. Current PALICC recommended the consideration of HFOV in patients with moderate-to-severe PARDS when plateau pressures exceed 28 cm H_2O in patients without significant chest wall compliance abnormalities. More data about the efficacy, safety, and optimal management strategies are needed.

11.5.1.4 Airway Pressure Release Ventilation (APRV)

APRV offers several theoretical benefits in the mechanical ventilation of PARDS patients. APRV has often been described as an extreme of inverse ratio ventilation. APRV facilitates oxygenation by sustaining a high pressure (P_{high}) for typically a few seconds (T_{high}). Ventilation occurs with spontaneous breathing during T_{high} as well as during a rapid and brief deflation to a low pressure (P_{low}), often a PEEP of 0 cm H_2O. A brief time (T_{low}) is spent at P_{low} to avoid alveolar derecruitment.

Potential advantages of APRV include the following:

- Oxygenation at lower peak airway pressures for a given tidal volume
- Minimizing overdistension while maximizing recruitment
- Preservation of spontaneous breathing
- Elimination of the need for neuromuscular blockade
- Little to no impact on hemodynamics
- Decreasing ventilator-patient dyssynchrony

Typically, the P_{high} is set at the plateau pressure observed in CMV, and the T_{high} is set at 4–6 s to maintain adequate oxygenation. P_{low} is usually set at 0 cm H_2O. This provides minimal resistance to exhalation during the release time. Use of a higher P_{low} may actually impede expiratory flow. Although often thought as the "PEEP," the P_{low} is not synonymous with PEEP. Instead, PEEP is generated by choosing the correct T_{low}, finding the right T_{low} is crucial in APRV. The optimal time spent at P_{low} should be insufficient to allow full exhalation and allow some intrinsic PEEP, *but also* allow sufficient CO_2 removal during the release. To find this optimal T_{low}, the expiratory flow pattern should be examined. The time it takes for expiratory flow to fall to 50% of the peak expiratory flow best approximates the initial T_{low} setting. Experience using APRV in adults suggests that the most significant benefits are achieved in the spontaneously breathing patient. A more extensive discussion of the mode and necessary adjustments based on gas exchange are found elsewhere in the text.

11.5.2 Improving Oxygen Delivery

A complete discussion of oxygen kinetics is covered in Chap. 2. Key equations regarding oxygen delivery in ARDS can be summarized as:

Oxygen delivery:

$$DO_2 = CaO_2 \times CI \times 10\,dL/L = 550 - 680\,mL/min/m^2$$

$$CaO_2(\text{approximated}) = Hgb \times 1.34\,mL\,O_2/g\,Hgb = 15-17\,mL/dL\,(\text{infant/child}), 16-20\,mL/dL\,(\text{adolescent})\,(\text{ignoring dissolved oxygen})$$

Oxygen consumption:

$$VO_2 = a - vDO_2 \times CI \times 10\,dL/L$$

$$VO_2 = (CaO_2 - CvO_2) \times CI \times 10\,dL/L = 120-200\,mL/min/m^2$$

While optimizing DO_2 and minimizing VO_2 may assist with oxygenation, supraphysiologic oxygen delivery is potentially harmful.

Strategies used to maintain DO_2 include correcting symptomatic anemia, correcting low cardiac output states, and maximizing oxygenation (SaO_2) as described above. Maintaining supranormal DO_2 with liberal use of blood transfusions and inotropes has no role in ARDS therapy and is likely detrimental. Treating fever and pain and preventing catabolism can minimize excessive VO_2. Intubation and mechanical ventilation also play a role for reducing VO_2 as up to 40% of cardiac output can be redirected to the respiratory muscles to maintain minute ventilation in ARDS at the expense of DO_2 to other organs.

11.5.3 Fluid Balance

The effect of fluid overload on lung function in the presence of ARDS is of ongoing interest. Early studies examining the nature of edema formation in the presence of diffuse lung injury demonstrated that the rate of edema formation is proportionate to pulmonary capillary pressure throughout the entire range from normal to elevated pressures. Thus, while in ARDS edema formation occurs in the absence of elevated pulmonary capillary pressures, the edema formation is not *independent* of pulmonary capillary pressure. In cardiogenic pulmonary edema, there is more of a threshold effect such that measurable pulmonary edema does not occur below a PAWP of 16–18. With pulmonary capillary injury, the rate of edema formation occurs at all levels of PAWP and is proportionate to PAWP.

Conservative fluid management with fluid restriction and initiation of diuretics when hemodynamically stable may shorten ventilator duration.

Traditionally, due to the application of high PEEP, patients were volume loaded to help overcome the decreases to venous return that occur with high PEEP. However, this approach neglected the physiology of edema formation as the fluid loading increases pulmonary edema formation. Early studies in intact animal models demonstrated that pulmonary function was improved with diuresis coupled with cardiac output support using inotropes or vasodilators. A multicenter randomized controlled clinical trial of conservative versus liberal fluid strategies in hemodynamically stable (minimal vasopressor/inotrope requirement) adults with ARDS was completed, demonstrating a marked difference in overall fluid balance between the two groups. There was improvement in multiple indices of pulmonary function as well as increased ventilator-free days (days alive and off mechanical ventilation) and fewer total ICU days for the conservative fluid strategy group. The protocol targeted lower CVP and PAWP in the conservative fluid management group with lower thresholds for the use of diuretics and inotropes.

When considering fluid balance, practitioners must balance the risk for pulmonary edema formation with the potentially beneficial effects of preload on oxygen delivery and organ perfusion. There remains a wide variability between fluid resuscitation strategies, the time to initiate vasoactive support to facilitate oxygenation delivery and organ perfusion, and when to use diuretics to achieve

desired fluid balance. Fluid balance should be a consideration during the management of PARDS, but more data is needed to help determine ideal fluid balance management strategy.

11.5.4 Prone Positioning

Prone positioning improves V/Q matching, recruits atelectatic dorsal lung units, and improves drainage of retained secretions.

Adult and initial pediatric data have shown that 65–85% of ARDS patients will have improved oxygenation when placed in the prone position. This improvement may be immediate (within 1 h) or delayed with improvement occurring over 24 h. Mechanisms for improved oxygenation are multifactorial and may include:

- Improved ventilation-perfusion matching. Chest CT scanning of the ARDS lung in adults demonstrates greater disease in dependent portions of the lung. In the supine position, perfusion is greatest in dependent areas, thus leading to greater V/Q mismatching. Prone positioning may transiently increase perfusion to less diseased lung segments.
- Redistribution of tidal volume to atelectatic areas. When placed prone, the patient's recruitment of atelectatic dorsal lung units allows for a more homogeneous distribution of gas throughout the diseased lung. This redistribution is often coincident with lower peak and plateau pressures.
- Improved diaphragmatic excursion by reducing effects of abdominal pressure, but only if the subject is spontaneously breathing.
- Improved postural drainage of secretions.

A randomized control trial of early proning in children with PARDS showed an improvement in oxygenation with the use of proning, but no differences in ventilator-free days or mortality between the prone and supine groups, and the study was stopped early for futility. A study in adults with moderate/severe ARDS (PaO_2/FiO_2 ratios <150) demonstrated significantly improved 28- and 90-day mortality in patients that were proned early in their ARDS course for at least 16 h daily. Prolonged prone positioning is reasonable to trial in moderate and severe PARDS in an attempt to improve oxygenation and V/Q matching, and potentially outcomes.

11.5.5 Corticosteroids

Corticosteroids should be used cautiously in PARDS given the risk of side effects, including immunosuppression, neuromuscular weakness, and re-intubation.

The use of corticosteroids in ARDS has been an active area of research and controversy. The vast majority of data has been derived from adult studies. Adult studies have shown both improved and worsened mortality with the use of methylprednisolone therapy. Due to the differences in timing of initiation, dose, and duration of corticosteroid use, there continues debate about the efficacy in ARDS. A meta-analysis in 2016 of multiple randomized trials demonstrated that patients randomized to receive corticosteroids had more unassisted breathing days. However, the initiation of corticosteroids after 14 days was associated with worse mortality, and all studies of corticosteroids noticed the potential for reinitiation of mechanical ventilation due to neuromuscular weakness. In a small randomized trial of methylprednisolone in PARDS, there were no significant differences in ventilator-free days or mortality. In a retrospective analysis of all steroid exposure in PARDS, steroid exposure >24 h was associated with fewer ventilator-free days, longer duration of ventilation, but no differences in mortality. PALICC recommends against the routine use of corticosteroids in PARDS at this time. Further investigation into the efficacy, dose, duration, and optimal time of initiation of corticosteroids is needed in PARDS.

11.5.6 Inhaled Nitric Oxide

Inhaled nitric oxide improves oxygenation by acting as a selective pulmonary vasodilator. It is unclear if it improves outcomes.

Multiple injuries including microvascular thrombosis, hypoxic vasoconstriction, and underdevelopment of both the pulmonary vascular bed and alveoli in patients with a history of prematurity can lead to elevated pulmonary vascular resistance and pulmonary hypertension in PARDS. The use of high PEEP may also worsen pulmonary hypertension. Inhaled nitric oxide (iNO) is a gaseous vasodilator that is rapidly inactivated by hemoglobin, thus making its vasodilatory actions restricted to the pulmonary vasculature. Theoretically, iNO may help improve V/Q matching. A multicenter randomized controlled trial showed that iNO only transiently improved OI and did not improve 28-day mortality but did reduce duration of mechanical ventilation. A second single-center cohort again showed a decrease in ventilator days in responders to iNO (≥20% improvement in OI or OSI by 6 h after iNO initiation). Again, no change was seen in overall mortality. Use of iNO may be considered in PARDS patients with pulmonary hypertension and those with severe oxygenation abnormalities.

11.5.7 Exogenous Surfactant

Despite initial promise, there is no utility to exogenous surfactant in PARDS. Appropriate delivery of surfactant may have complicated efficacy studies.

The use of exogenous surfactant preparations is standard therapy for neonates with respiratory distress syndrome. Even though endogenous surfactant is both quantitatively decreased and qualitatively dysfunctional, multiple studies examining a variety of surfactant replacements in adult ARDS have all yielded negative results. Initial studies in PARDS showing encouraging results for surfactant replacement were confounded by an imbalance in the number of immunocompromised subjects between treatment arms. A more recent large multicenter randomized trial was stopped early for futility and showed no benefit to oxygenation or mortality with exogenous surfactant, although this may have to do with how surfactant was delivered. The CALIPSO trial focused on the use of surfactant in a subset of PARDS patients with leukemia, lymphoma, or after hematopoietic stem cell transplant and again did not show differences in outcomes between the treatment and placebo group and was stopped early for low enrollment. Thus, as of now, no data support the use of surfactant replacement therapy in PARDS.

11.5.7.1 Neuromuscular Blockade

Neuromuscular blockade improves oxygenation and ventilation by limiting the damaging and insidious effects of ventilator dyssynchrony.

Use of neuromuscular blockade (NMB) during PARDS has potential advantages. The most discussed advantage is limiting patient-ventilator dyssynchrony when sedatives alone are not adequate, thus mitigating double triggering and unintentionally high volumes and pressures contributing to VILI. In addition, NMB facilitates titration to permissive hypercapnia and the use of high-frequency ventilation strategies. Disadvantages include lack of spontaneous breathing contributing to diaphragmatic and respiratory muscle wasting and concerns about contribution of NMB to critical care myopathy and lasting muscle weakness. The ACURASYS trial showed improvement in 90-day mortality without an increase in ICU-associated muscle weakness in adult ARDS subjects (PaO_2/FiO_2 ratios <150) who received 48 h of neuromuscular blockade with cisatracurium early in the course of severe ARDS. No randomized trials of NMB exist specifically for PARDS. It is reasonable to consider NMB early in the course of PARDS as we await a definitive trial in pediatrics.

11.5.8 Extracorporeal Membrane Oxygenation (ECMO)

ECMO should be considered for refractory severe PARDS, especially when ventilator settings and airway pressures are escalating and becoming potentially more damaging.

Children who have progressive respiratory failure despite maximal conventional therapies should be considered for extracorporeal membrane oxygenation (ECMO). In patients that do not have a contraindication for ECMO, OI > 40 is often used as a trigger for initiation, although this varies considerably between institutions. ECMO can be used to both oxygenate and efficiently clear carbon dioxide. Both venoarterial (VA) and veno-venous (VV) ECMO have been used successfully for ARDS, with worldwide experience and comfort with the modality for ARDS increasing after the 2009 H1N1 influenza epidemic. VV-ECMO is often preferred even for patients with cardiovascular dysfunction that is felt to be causally related to the lung injury. In adults, the CESAR trial randomized patients with severe ARDS to referral to ECMO center or continued care. Patients referred to ECMO center showed reduction in mortality or severe disability at 6 months. However, only 75% of those referred to an ECMO center went on ECMO, which leaves open the possibility that ECMO in of itself did not improve outcomes, but the advanced care bundle offered by an ECMO center was the important factor. Recently, a randomized control was halted early due to pre-study futility rules of the primary outcome of mortality at 60 days. Patients were randomized to early VV-ECMO versus conventional therapy, with the opportunity for subjects on conventional therapy to cross over to ECMO. At the time of study termination, the 60-day mortality was 35% for the early ECMO group and 46% in the conventional treatment group, with a relative risk of 60-day mortality of 0.76 [CI 0.55–1.04, $p = 0.09$]. The decision to stop early was heavily criticized. Even with this negative trial, ECMO remains a consideration in severe ARDS. ECMO survival after prolonged mechanical ventilation (particularly > 14 days) has been shown to be poor. For this reason, its use should be considered early in the course of refractory PARDS. No randomized trials exist for ECMO in severe PARDS. PALICC recommends the early consideration of ECMO for severe PARDS.

11.6 Summary

PARDS management has, to date, largely been extrapolated from adult ARDS management, with presumed commonalities in etiology, pathogenesis, and outcomes. However, emerging data suggest that PARDS possesses a distinct epidemiology and outcome profile, with risk factors, etiologies, comorbidities, and outcomes specific to pediatrics. This makes extrapolation of adult ARDS data challenging. Specific studies are needed to advance our understanding of PARDS and explicit comparisons made with adult ARDS. In the interim, a lung-protective approach limiting excessive distending pressures, use of PEEP, and conservative fluid management seem to be reasonable approaches to PARDS, with judicious, thoughtful application of ancillary therapies, carefully weighing risks and benefits in the absence of definitive evidence.

Review Questions

1. Which statement is true regarding the pathophysiology of PARDS?
   A. High V/Q units and intrapulmonary shunting are responsible for the hypoxia.
   B. Lung compliance, defined as $\Delta P/\Delta V$, is reduced in PARDS.
   C. Functional residual capacity is reduced in PARDS due to proteinaceous edema and surfactant dysfunction.

D. The pressure-volume loop is more steep in a child with PARDS than in a healthy child.
E. The thickening of the alveolar-endothelial barrier is a primary cause of diffusion impairment and hypoxia in ARDS.

2. A 4-year-old female was found unresponsive in a pool. During her first day in the PICU, she has required escalation of her mechanical ventilatory support to a PEEP of 12 cm H_2O and an FiO_2 of 70% to maintain saturations of 90%. Her current peak inspiratory pressure is 35 cm H_2O to reach a tidal volume of 6 mL/kg. Which of the following is an accurate description of her pulmonary biomechanics?
   A. High elastance, low compliance, and high functional residual volume
   B. Low compliance, low elastance, and predominately low V/Q mismatched lung units
   C. High compliance, low elastance, and high functional residual volume
   D. Low compliance, high elastance, and predominately low V/Q mismatched lung units
   E. High elastance, low compliance, and high resistance

3. Which of the following is true regarding early therapies in ARDS in light of its physiologic derangements?
   A. Aggressive treatment of hypercarbia may attenuate the ARDS course.
   B. Application of 100% FiO_2 is often sufficient to overcome the hypoxia.
   C. Early use of inotropic agents and diuretics may rapidly reduce ongoing edema formation.
   D. The use of PEEP is to maintain the lungs at a low functional residual volume.
   E. The early and titrated application of a high-PEEP, low-tidal volume strategy can improve oxygenation while limiting ventilator-induced lung injury.

4. Which statement concerning PARDS and mechanical ventilation is true?
   A. High-frequency oscillatory ventilation is recommended for children with refractory hypercarbia despite conventional mechanical ventilation.
   B. High PEEP levels help to increase functional residual volume but worsen V/Q matching.
   C. Prone positioning during mechanical ventilation is used to improve V/Q matching and has improved both oxygenation and mortality in PARDS.
   D. A high-PEEP, high-tidal volume strategy allows for permissive hypercapnia and reduces ventilator-associated lung injury.
   E. A high-PEEP, low-tidal volume strategy is helpful in both improving lung unit recruitment by increasing functional residual volume and limits barotrauma.

5. What are the theoretical benefits of high-frequency oscillatory ventilation in PARDS?
   A. Improved mobilization of airway secretions.
   B. Allows for oxygenation at a set mean airway pressure and ventilation with small tidal volumes at fast rates.
   C. Ventilation is a completely passive process.
   D. Preservation of spontaneous breathing.
   E. Due to the sustained mean airway pressure, the effect on venous return is less than conventional ventilation.

6. Which of the following statements is true regarding adjunctive therapies for ARDS?
   A. Corticosteroids have been shown to improve mortality in PARDS.
   B. ECMO is most effective in patients that have been mechanically ventilated at least 20 days.
   C. Nitric oxide therapy improves oxygenation and reduces ventilator days in PARDS.
   D. Prone positioning may transiently improve oxygenation and has shown improved survival in adult ARDS.
   E. The use of surfactant therapy is proven to benefit patients with lymphoblastic leukemia who develop PARDS.

7. A 3-year-old male develops progressive PARDS after sepsis from an intra-abdominal infection. The patient is on HFOV with a mean airway pressure of 30 cm H_2O, 7 Hz, and an amplitude of 90. The patient is on 75% FiO_2 with saturations of 82%. Arterial blood gas result: pH 7.35, PCO_2 70 mmHg, and PaO_2 40 mmHg
   The most appropriate intervention would be to:
   A. Increase the mean airway pressure to improve oxygenation while making considerations for ECMO
   B. Decrease the hertz to improve ventilation
   C. No changes
   D. Increase the FiO_2 and make no other changes
   E. Increase the mean airway pressure and give surfactant

8. A 22-month-old has progressed to PARDS after pneumonia. He has just been escalated on his ventilator support. He is on pressure-regulated volume control with a tidal volume of 6 mL/kg and a PEEP of 12 cm H_2O and has resulted in a mean airway pressure of 17 cm H_2O. He is on 55% FiO_2. His most recent ABG showed a pH of 7.29, a $PaCO_2$ of 65 mmHg, and a PaO_2 of 50 mmHg. He is on no vasoactives, and he is 1000 mL positive for the last 48 h. Which of the following is most correct?
   A. His oxygenation index is 19. Ventilation should be increased by increasing the tidal volume.
   B. His oxygenation index is 11. He has moderate PARDS, and no changes are needed.
   C. His oxygenation index is 19. He has severe PARDS and should be started on diuretics.
   D. His oxygenation index is 19. The patient has moderate PARDS and should be started on nitric oxide.
   E. His oxygenation index is 11. He has moderate PARDS, and PEEP should be increased to 14 cm H_2O.

Answers

1. C
2. D
3. E
4. E
5. B
6. D
7. A
8. C

Suggested Readings

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Conventional Mechanical Ventilation

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Contents

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Learning Objectives

- Describe the differences between negative and positive pressure ventilation.
- Describe the effects of positive pressure ventilation on the respiratory system.
- Describe the effects of positive pressure ventilation on preload and afterload.
- Describe how the main ventilation characteristics impact oxygenation.
- Describe how the main ventilation characteristics impact ventilation and CO_2 clearance.
- Describe the differences between pressure and volume modes of ventilation.
- Detail the mechanisms of ventilator triggering.
- Detail the different methods of ventilator cycling.
- Describe the methods of delivering assisted breaths.
- Understand how to determine the main ventilator settings.
- Describe the benefit and risk of the patient's spontaneous contribution during mechanical ventilation.
- Describe ventilator strategies to minimize ventilator-induced lung injury and diaphragm dysfunction.
- Detail weaning strategies and extubation readiness assessment.
- Describe the monitoring of mechanical ventilation.

12.1 Introduction

Respiratory failure is one of the main reasons for admission to a pediatric intensive care unit (PICU). About half of the patients admitted to the pediatric intensive care unit (PICU) need a ventilator support. Before the 1930s, respiratory failure was uniformly fatal due to the lack of equipment and techniques for airway management and ventilator support. The use of mechanical support for respiratory failure began with negative pressure ventilation during the poliomyelitis epidemics. Technological progress over time has allowed the widespread use of positive pressure ventilation. This vital support technology has dramatically changed the outcome of pediatric respiratory failure, which now carries a low mortality rate. The performance of ventilators has improved, allowing a better control of delivered ventilation, increased safety, and the development of many ventilation modes. The complexity of the mechanical ventilation options has increased in parallel with the complexity of the PICU population, and the management of ventilator support can sometimes seem overwhelming. In that context, it is essential for the PICU clinicians to understand the functioning and the impact of conventional mechanical ventilation on the critically ill children.

This chapter reviews the main physiological features of respiratory failure and the basic principles of conventional mechanical ventilation to understand the pathophysiological impact of mechanical ventilation. Based on this background, we will describe a logical approach of the initial setup and adjustment of mechanical ventilation in children. The importance of monitoring for mechanically ventilated children will then be described.

12.2 Pulmonary Physiology and Conventional Mechanical Ventilation

12.2.1 Indications for Mechanical Ventilation and Mechanisms of Respiratory Failure

The primary goals of mechanical ventilation are the maintenance of adequate oxygenation and clearance of CO_2 from the body in the amount needed to maintain cellular homeostasis. A diverse group of disease processes, involv-

Table 12.1 Main indications and objectives for airway control and mechanical ventilation

Indications	Main objectives
Respiratory system disorders	
- Pulmonary parenchymal disease	Improvement of hypoxemia and ventilation
- Airway problems	Airway control
- Upper or lower airway obstruction	Ventilation improvement
- Respiratory muscle failure	Ventilation improvement/respiratory unloading
Cardiovascular failure	Respiratory unloading/LV afterload reduction/preload optimization
Alteration in the central control of breathing	
- Deep sedation or analgesia (i.e., postoperative period, trauma)	Control of airway and ventilation
- Altered mental status	Control of airway and ventilation

ing the respiratory, cardiovascular, and central nervous systems, may lead to respiratory failure. The primary indications for endotracheal intubation and mechanical ventilation in the PICU are described in Table 12.1. The objective of the institution of mechanical ventilation varies depending on the disease categories and the respective importance of hypoxemia, hypercarbia, hemodynamic, and neurological status.

12.2.2 Pathophysiology of Hypoxemia and Application to Mechanical Ventilation

The primary cause of hypoxemia in the PICU patients is ventilation-perfusion inequality related to acute lung injury and pulmonary parenchymal disease.

When confronted with the hypoxemic patient, understanding the etiology of hypoxemia is crucial to tailor the management of mechanical ventilation. The primary cause of hypoxemia in the PICU patient is ventilation-perfusion inequality related to acute lung injury and pulmonary parenchymal disease. Both ventilation and perfusion are not uniform in the normal lungs due to pleural pressure gradient and gravity. The ventilation-perfusion (V/Q) ratio is also not homogenous, higher in the apical and lower in the basal regions, leading to a normal global V/Q ratio of about 0.8. In acute pulmonary parenchymal disease, regions with low V/Q ratio generate hypoxemia, when the protective mechanism of hypoxic pulmonary vasoconstriction is overwhelmed.

Other mechanisms can be involved less frequently in hypoxemia: right-to-left shunt, impairment of diffusion capacity, and hypoventilation. Limitation of diffusion capacity is not frequent in acute disease but could occur in complex lung disease. Hypercapnia is usually uncommon in that context in that CO_2 diffuses much faster than oxygen and minute ventilation is normally increased by the hypoxemia-mediated ventilation response. Hypoventilation alone does not produce significant hypoxemia in a healthy lung. However, hypoxemia can occur in case of lung disease or in profound hypoventilation. Another issue that must be considered when caring for hypoxemic patients with ventilation-perfusion mismatch or true shunt is the impact of low mixed venous blood

saturation. Improvement in mixed venous oxygen saturation may also improve arterial oxygen saturation in that context.

In the setting of hypoxemia, the severity of the lung disease may be estimated by the difference between the PaO_2 and the partial pressure of oxygen in the alveoli, the A-a or alveolar-arterial oxygen gradient. The A-a gradient is normally <10 mmHg, and it reflects the integrity of the alveolocapillary membrane and effectiveness of gas exchange. Widened gradient is observed in case of hypoxemia due to V/Q mismatch, diffusion limitation, and shunt, whereas it is normal in case of hypoventilation. Several indices are also used to diagnose and assess the severity of pediatric acute respiratory distress syndrome (PARDS). The oxygenation index (OI = mean airway pressure × FiO_2/PaO_2 × 100) and the ratio of the PaO_2 to FiO_2 (P:F ratio) are both associated with PARDS severity and mortality, and both require an arterial blood gas. In absence of arterial blood gas, the noninvasive oxygenation saturation index (OSI = mean airway pressure × FiO_2/SpO_2 × 100) and SpO_2 to FiO_2 ratio (S:F ratio) can be used as good alternatives of OI and P:F ratio, respectively, provided a SpO_2 of 97% or lower.

Mean airway pressure is the primary determinant of oxygenation, FiO_2 being the second evident determinant. Mean airway pressure can be calculated as the area under the curve of the pressure-time curve. It is therefore mainly determined by the positive end-expiratory pressure (PEEP), the peak inspiratory pressure (PIP), and the inspiratory time. Increasing the mean airway pressure by manipulation of any of these variables will recruit alveoli, improve ventilation-perfusion matching, and decrease intrapulmonary shunting. In addition, increasing mean airway pressure may also result in a significant improvement in respiratory compliance, thereby allowing lower driving pressure (difference between inspiratory and expiratory pressures) to obtain a similar tidal volume, as illustrated in Fig. 12.1.

Mean airway pressure is the primary determinant of oxygenation. It is mainly determined by the positive end-expiratory pressure (PEEP), the peak inspiratory pressure (PIP), and the inspiratory time.

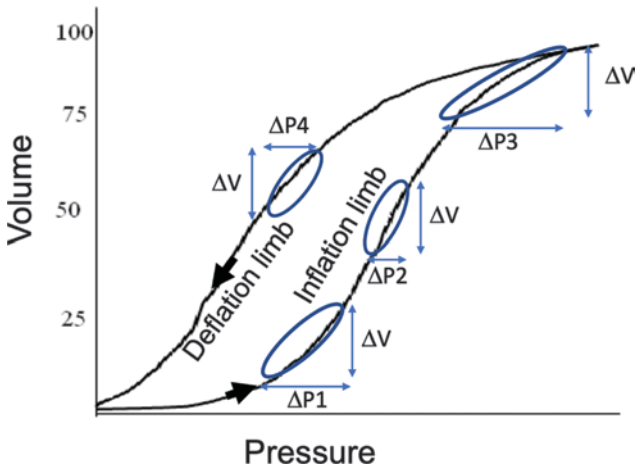

Fig. 12.1 Schematic representation of the respiratory pressure-volume curve. The larger curve represents the entire excursion of the lung volume from a pressure of zero to a maximal pressure. The smaller loops illustrate pressure-volume curves generated with similar and physiologic tidal volumes (ΔV), at different levels of PEEP. The respiratory system compliance (ΔVolume/ΔPressure) can be illustrated as the local slope of the pressure-volume curve. The compliance decreases at each extreme of the ascending limb of the curve, reflecting the overinflation (right extreme, loop 3) and the atelectasis (left extreme, loop 1), as illustrated by the larger ΔPressure observed for similar ΔVolume. The fourth small loop illustrates the interest of ventilating the lung on the deflation limb of the pressure-volume curve, with both a good compliance (relatively small ΔP4) and a large lung aeration, while the level of pressure is smaller than for the loop 1. To go from loop 2 to loop 4 requires a recruitment maneuver

The restoration or preservation of functional residual capacity (FRC) above the closing capacity (CC, the volume at which small airway closure occurs during expiration) is critical in the maintenance of a normal V/Q ratio.

The restoration or maintenance of functional residual capacity (FRC) above the closing capacity (CC, the volume at which small airway closure occurs during expiration) is critical in the maintenance of a normal V/Q ratio. Conditions that decrease FRC below CC (or increase CC above FRC) result in a maldistribution of ventilation-perfusion and adversely affect the mechanics of breathing (► Box 12.1). In conditions associated with a decreased FRC (i.e., pulmonary edema, pneumonitis, PARDS), increasing PEEP is the most logical measure to increase FRC (see below for a full discussion regarding PEEP). In situations associated with increased CC (i.e., bronchiolitis, reactive airway disease), strategies to reduce CC should also be considered (i.e., etiological treatment, bronchodilators, secretions clearance).

Box 12.1 Factors affecting functional residual capacity and closing capacity

Reduced functional residual capacity:

- Acute lung injury/acute respiratory distress syndrome (ARDS)
- Near drowning
- Acute pneumonia
- Pulmonary edema
- Radiation pneumonitis
- Atelectasis
- Supine position
- Abdominal distention
- Obesity

Increased closing capacity:

- Bronchiolitis
- Asthma
- Bronchopulmonary dysplasia
- Smoke inhalation with thermal injury to airway
- Cystic fibrosis
- Tracheomalacia
- Infancy

12.2.3 Pathophysiology of Ventilation Failure (Hypercarbia) and Application to Mechanical Ventilation

The $PaCO_2$ is the result of the equilibrium between CO_2 clearance (by the ventilation) and the body's production of CO_2. In most clinical circumstances, the control of $PaCO_2$ will rely on the control of the minute ventilation, defined as RR times V_T.

One major aim of mechanical ventilation is to provide minute ventilation (respiratory rate [RR] x the tidal volume [V_T]) that is adequate for CO_2 removal. The $PaCO_2$ is the result of the equilibrium between CO_2 clearance (by the ventilation) and the body's production of CO_2 during the energy metabolism. In most clinical circumstances, the control of $PaCO_2$ will rely on the control of the minute ventilation. However, some control of the body's endogenous CO_2 production is possible through the increase in the use of fats versus carbohydrates for nutrition, avoidance of overfeeding, or by control of body temperature. Sedation, prevention of hyperthermia, and even induction of mild hypothermia can also facilitate the control of hypercarbia and limit mechanical ventilation requirements.

Although minute ventilation is defined as RR times V_T, not all of the V_T is involved in effective gas exchanged. That part of V_T that does not participate in gas exchange is referred to as physiologic dead space. Total or physiologic dead space is composed of anatomic dead space (that area of the conducting areas or the trachea and bronchi that do not participate in gas exchange)

and alveolar dead space (those alveoli which are ventilated but not perfused). In the healthy state, the alveolar dead space is minimal so that anatomic and physiologic dead space are approximately the same. Although anatomic dead space, representing approximately 30% of a normal tidal breath or 150 mL in an average-sized adult, does not generally change regardless of the disease process, alveolar dead space may change significantly in patients with pulmonary parenchymal disease, with pulmonary vascular disease, or with changes in cardiac output resulting in alterations in pulmonary perfusion. The latter principle is clearly demonstrated by the abrupt decline in end-tidal CO_2 ($ETCO_2$) that occurs with cardiac arrest, a decrease in cardiac output, or pulmonary embolism. Of note, anatomic dead space tends to augment with younger age.

Dead space ventilation (V_D) refers to ventilation that does not participate in gas exchange. Since the anatomic dead space is relatively constant in patients with healthy lungs, increasing the V_T decreases the ratio of V_D to V_T. In effect, the increased V_T increases alveolar ventilation. It is also the case in most patients with mild to moderate lung disease that alveolar dead space is relatively fixed and that changes in V_T primarily affect alveolar ventilation. Thus, in most cases, a 10% increase in V_T will result in a greater than 10% improvement in effective minute ventilation, such that small increases in V_T are more effective at ventilating than the same proportionate increases in rate. However, in some patients with severe lung disease, ventilation of poorly perfused regions of the lungs (alveolar V_D) can be significant. In this setting, increases in V_T may not decrease V_D/V_T since higher alveolar pressures as a result of larger V_T may result in a further decrease in pulmonary perfusion and increase in alveolar V_D. An estimation of the effect of changes in V_T on V_D/V_T in such clinical scenarios can be provided by estimating V_D/V_T using capnography with $ETCO_2$ measurements. The alveolar dead space fraction (AVDSf) can be estimated using the following equation:

Dead space ventilation (V_D) refers to ventilation that does not participate in gas exchange.

$$\text{AVDSf} = \left(\text{PaCO}_2 - \text{P}_{\text{ET}}\text{CO}_2\right) / \text{PaCO}_2 \quad \left(\text{P}_{\text{ET}}\text{CO}_2 = \text{end} - \text{tidal}\,\text{PCO}_2\right)$$

The alveolar dead space fraction is an important severity marker and is dependently associated with mortality in pediatric acute respiratory distress syndrome.

We can summarize that a change in the metabolic rate with an alteration in CO_2 production, a change in minute ventilation (RR or V_T), or a change in V_D may affect $PaCO_2$. Importantly, ventilation to normocarbia is not necessary and may in fact be harmful, especially in patients with severe lung disease. Current practice includes the use of permissive hypercarbia. The Pediatric Acute Lung Injury Consensus Conference (PALICC) recommended maintaining pH 7.15–7.30 within lung protective strategy in moderate to severe PARDS, except in patients with intracranial hypertension, severe pulmonary hypertension, select congenital heart disease lesions, hemodynamic instability, or significant ventricular dysfunction.

12.2.4 Impact of MV on the Respiratory and the Cardiovascular Systems

Although a lifesaving technology, mechanical ventilation may also have a negative impact on the respiratory system. Ventilation-induced lung injury (VILI) originates from several mechanisms, including volutrauma (the injury caused by alveolar overdistention), atelectrauma (injury due to repeated opening/closure of lung units), barotrauma (consecutive to elevated transpulmonary pressures), and biotrauma (following the release of mediators that can aggravate preexist-

Ventilation-induced lung injury (VILI) originates from several mechanisms, including volutrauma, atelectrauma, barotrauma, and biotrauma.

ing lung injury). A review about VILI incidence and mechanisms is beyond the scope of this chapter. However, it is important to acknowledge that although there is clinical evidence that VILI exists in the pediatric population and that protective lung volume ventilation should be recommended, it remains a field which has been much less studied than in adults. In particular, no large randomized controlled trial assessing the impact of low V_T has been conducted in the PICU. Most components of the ventilation strategy in pediatric patients are therefore based on concepts originating from studies conducted in the adult population. This is particularly important since experimental animal data tends to suggest that the pediatric population may be less sensitive to VILI mechanisms.

Complete assistance by mechanical ventilation, with suppression of the spontaneous respiratory activity, is associated with a rapid diaphragm dysfunction (ventilation-induced diaphragm dysfunction, VIDD).

One goal of mechanical ventilation is to support the respiratory muscles in case of respiration failure, usually associated with a high work of breathing and a risk of diaphragm fatigue. It is, however, clear that complete assistance, with suppression of the spontaneous respiratory activity, is associated with rapid diaphragm dysfunction (ventilation-induced diaphragm dysfunction, VIDD). In adult populations, decreased diaphragm force and atrophy of diaphragm fibers are observed as early as in the first 24 hours and deteriorates further in the absence of spontaneous breathing activity. The dynamic of VIDD in the PICU has been less extensively studied, although diaphragm atrophy has also been reported in infants. The diaphragmatic force is one major factor of extubation success, and maintaining diaphragm function and activity should therefore be an important focus during mechanical ventilation. Importantly, the clinical assessment of the patient breathing activity during mechanical ventilation is not easy. Physiologic studies based on monitoring of esophageal pressure or diaphragm electrical activity have shown that blunted respiratory drive is highly prevalent in the PICU, even at very low levels of support and when the clinical team thought that the patient was actively breathing.

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Pulmonary vascular resistance is increased when the lung is collapsed and is minimized (optimized) when the lung is inflated to normal functional residual capacity.

The effects of mechanical ventilation on the cardiovascular system are complex and highly dependent on a patient's underlying condition. The basic hemodynamic effects of mechanical ventilation are as follows. During positive pressure ventilation, the output of the right ventricle decreases during inspiration while at the same time, the output of the left ventricle increases. The opposite occurs during a spontaneous or negative pressure breath; right ventricular output transiently increases, and left ventricular output decreases. The effects on left ventricular output are felt to be primarily a consequence of changes in afterload. A positive pressure breath decreases left ventricular transmural pressure, while a negative pressure breath does the opposite, increasing LV transmural pressure. Overall, positive pressure ventilation often results in decreased cardiac output due to decreases in systemic venous return and LV preload and an increase in RV afterload. The effects of positive pressure ventilation on preload are most frequently not wanted, and they may be compensated by increasing intravascular volume through fluid loading. Preload reduction may, however, be a positive effect in patients with fluid overload or congestive heart failure. Patients with normal cardiovascular function can tolerate the effects of positive pressure ventilation with little compromise in the absence of dehydration or intravascular volume depletion. However, the initiation of positive pressure ventilation in the face of hypovolemia, including warm septic shock, can have catastrophic hemodynamic consequences, and one should always be ready to volume load such patients at the time of intubation. Patients with cavo-pulmonary anastomosis who are dependent on passive pulmonary blood flow can be highly sensitive to the application of positive pressure ventilation due to decreased systemic venous return and pulmonary blood flow.

The normal pulmonary vascular bed has low pressure and resistance. Critical illness and especially pulmonary disease can increase pulmonary vascular resistance (PVR) through hypoxic vasoconstriction, acidemia, and the release

of vasoactive mediators. Variables relating to lung inflation may also affect pulmonary vascular resistance through maintenance of normal lung volumes, ventilation-perfusion matching, and minimizing hypoxemia. Pulmonary vascular resistance is increased when the lung is collapsed and is minimized (optimized) when the lung is inflated to normal functional residual (FRC) capacity. The increased PVR at low lung volumes is a result of the combination of hypoxic pulmonary vasoconstriction and some compression of extra-alveolar blood vessels. With lung inflation, the extra-alveolar vessels are held open by adjacent connective tissue. If the lung is inflated much above normal FRC, pulmonary vascular resistance increases as a result of the compression of the alveolar capillary bed within overdistended alveoli. From a purely mechanical perspective, the initiation of positive pressure ventilation with high levels of PEEP can result in decreased cardiac output by virtue of both mechanisms: decrease in systemic venous return and increased pulmonary vascular resistance. These effects are well tolerated in the presence of normal RV function but may be significant in the patient with RV dysfunction or single ventricle with the absence of a right-sided pumping chamber. To the extent that the institution of positive pressure ventilation with therapeutic levels of PEEP can result in the correction of hypoxemia and respiratory acidosis, these beneficial effects on right ventricular performance can counteract the negative mechanical effects. Thus, even in the patient with severe RV dysfunction or Fontan physiology, improving oxygenation and ventilation with the normalization of functional residual capacity can result in decreased PVR and improved cardiac output.

The initiation of positive pressure ventilation with high levels of PEEP can result in decreased cardiac output by virtue of both mechanisms: decrease in systemic venous return and increased pulmonary vascular resistance.

The influence of positive pressure ventilation on the left ventricular performance is multifactorial. As mentioned above, during positive pressure inspiration, LV afterload is affected by intrathoracic pressure acting on the external wall of the LV. The transmission of positive airway pressure to the mediastinum and the external surface of the left ventricle decreases the transmural pressure of the LV, thus decreasing LV afterload. In addition, during the inspiratory phase of a positive pressure breath, LV preload is increased as the positive pressure applied to the lungs aids in emptying the pulmonary veins into the left atrium. The effect of improved LV systolic function during inspiration is most pronounced in patients with LV dysfunction. These patients also benefit from redistribution of limited cardiac output and oxygen delivery by virtue of decreased work of breathing and thus decreased need to provide oxygen for the respiratory muscle work. The proportion of cardiac output which is normally dedicated to the respiratory muscles is small, close to 5%. In case of respiratory failure (including in patients with cardiogenic pulmonary edema), the respiratory muscles consumption increases, and the proportion of cardiac output used by the respiratory system can exceed 30%. Reducing the work of breathing in these patients is therefore essential.

During positive pressure, LV preload is increased, LV afterload is decreased, and RV afterload is increased.

The complex cardiopulmonary dynamics during positive pressure ventilation can be demonstrated at the bedside through the observation of systolic pressure variation in the arterial line waveform occurring during the respiratory cycle.

12.3 Basics of the Ventilator Functioning

12.3.1 Negative Pressure Ventilation

With the poliomyelitis epidemics of the 1930s, negative pressure ventilation was introduced to support patients with neuromuscular weakness leading to acute and chronic respiratory failure. The negative pressure ventilators ("iron lungs") were large tanks into which the patient's entire body was placed (Fig. 12.2). The patient's neck was surrounded by a rubber mat with a small

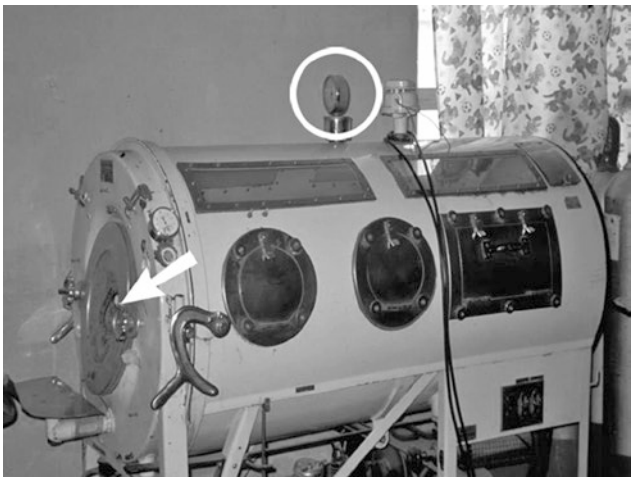

Fig. 12.2 Photograph of a negative pressure ventilator otherwise known as the "iron lung." These devices were used during the poliomyelitis epidemics of the 1930s and 1940s for the treatment of acute and chronic respiratory failure. The rubber sheet with a small opening in the middle (*arrow*) was placed over the patient's head to ensure an airtight seal. The amount of subatmospheric pressure was indicated on the pressure gauge on the top of the tank (*circle*)

opening in the center through which the patient's head protruded. The driving force was a piston located at the bottom of the tank. A downward movement of the piston caused an increase in the volume of the container, creating a negative pressure around the patient's thorax. The negative pressure resulted in the expansion of the chest wall, with air entry through the patient's airway into the lung. Although somewhat effective in patients with respiratory failure related to muscle weakness, there were significant limitations in the amount of negative pressure that could be generated, and as such, these devices were not effective in patients with significant alterations in respiratory compliance or resistance. Additionally, the devices were bulky, restricted access to the patient, and could not be used in patients with airway disease.

Iron lungs hold a place in the medical history, but negative pressure ventilation is still being used and available in the modern era. Large containers have been replaced by cuirass or vests that fit over the patient's thorax and are sealed at the waist and neck. The air within the jacket is intermittently evacuated, thereby creating a negative pressure (compared to the atmosphere). The support can be delivered as a constant negative pressure or with intermittent positive pressure cycles to facilitate exhalation. These devices could be used for home care and found their greatest use in patients with chronic respiratory insufficiency due to neuromuscular weakness but are also sometimes used in acute conditions. Negative pressure ventilation can be used alone or in combination with other type of support, like high-flow nasal cannula or noninvasive ventilation.

The advantages of negative pressure ventilation are that it does not require endotracheal intubation, it can be applied intermittently, it can be used at home without the need for tracheostomy, and it avoids the impact of positive pressure ventilation on cardiovascular system (preload reduction and right afterload increase). This may be particularly interesting in children following cavo-pulmonary anastomoses. In the postoperative setting of these surgeries, positive pressure ventilation can significantly decrease the passive pulmonary blood flow. Although the ideal strategy is to attempt early tracheal extubation, negative pressure ventilation could be an interesting alternative when extubation is not possible.

Negative pressure ventilation also has disadvantages. The delivered support is not synchronized with the patient breathing. In case of abnormal airway with inspiratory resistance, the negative pressure ventilation can exacerbate the respiratory distress. Finally, the fact that no positive pressure is applied in the airway can be perceived as better for the impact on the lung and VILI, but this is not absolutely true. Indeed, the transpulmonary pressure (difference between alveolar pressure and pleural pressure) is the variable that best reflects the lung strain and the risk of VILI. Increasing transpulmonary pressure either by a positive pressure in the alveoli (positive pressure ventilation) or by a negative pressure in the pleura (negative pressure ventilation) can both increase the lung strain and expose to the risk of VILI.

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12.3.2 Positive Pressure Ventilation

As opposed to negative pressure ventilation, during positive pressure ventilation, the inspiratory flow is achieved by the increase in the airway pressure, which generates a pressure gradient from airway to the alveoli. This increases the transpulmonary pressure by increasing the alveolar pressure rather than by decreasing the pleural pressure. Positive pressure ventilation therefore requires an airway interface, mostly endotracheal tube or tracheostomy for conventional ventilation. Noninvasive positive pressure ventilation can also be delivered with a nasal, oronasal, or facial mask, nasal cannula or prongs, or a helmet. In this chapter, we focus on conventional invasive positive pressure ventilation.

When the decision has been made to initiate mechanical ventilation, the clinician will be faced with the following decisions: (a) the mode of ventilation (how the ventilator cycles are determined); (b) the controlled variable (pressure or volume) which will control the tidal breath; (c) the specific ventilator settings, including the magnitude of the controlled variable (inspiratory pressure or tidal volume), the PEEP, the inspiratory time and the ventilator rate, the trigger sensitivity, and the FiO_2; and (d) the alarm settings.

12.3.3 The Different Ventilation Modes

The era of positive pressure ventilation began with controlled mandatory ventilation (CMV) which provided intermittent positive pressure breaths to the patient without the ability to sense the patient's own respiratory efforts and no gas flow in between the ventilator breaths. This provided no means to allow the patient to breath spontaneously, resulting in significant patient-ventilator asynchrony unless deep levels of sedation or neuromuscular blockade were used. CMV was followed by intermittent mandatory ventilation (IMV) which provided a set number of breaths/min provided at a specific interval but also allowed for spontaneous ventilation through the use of a continuous gas flow or a demand valve. Despite the ability to allow spontaneous ventilation, the IMV mode did not synchronize the ventilator breath with the patient's effort, and there was no assistance during the spontaneous breaths. With the development of technology for sensing the patient's respiratory efforts, strict IMV has been replaced by modes such as assist control (AC) and synchronized intermittent mandatory ventilation (SIMV). Both AC and SIMV modes deliver a set number of mandatory ventilator "full" breaths, determined by the set respiratory frequency and the set volume or pressure, synchronized with the patient's effort. If the patient breathes above the set minimal frequency, there will be additional minute ventilation from this spontaneous ventilation.

In SIMV, the additional breaths can be allowed with no added support (SIMV alone) or can be assisted according to pressure support (SIMV-PS) or volume support (SIMV-VS) principle (see below). In assist control, every additional detected breath will lead to a full ventilator breath. The theoretical advantage of AC ventilation is that the patient receives a similar support for each breath. However, if the spontaneous respiratory frequency is excessively high or in case of auto-triggering, the risk of overassistance and of expiratory flow limitation with overdistension may be higher. Of note, those risks also exist in SIMV, and in both modes, it is essential to avoid auto-triggering and limit unnecessary tachypnea. There is also a belief that with SIMV, weaning may be facilitated by the possibility of decreasing either the frequency or the level of support. However, studies in adults rather suggest that this complexity prolongs the weaning duration.

In its earliest forms, triggering was accomplished by detecting a pressure change in the ventilator circuit (usually −1 to −3 cm H_2O). Further refinement of patient effort sensing relies on detection of flow differences between the inspiratory and expiratory limbs of the ventilator circuit (flow triggering). Available now in all new critical care ventilators, flow triggering requires less patient work and is more comfortable than pressure triggering. The trigger setting can be difficult. Setting the threshold too high may lead to failure to sense the patient's spontaneous efforts ("wasted efforts'"). Setting the trigger threshold too low (too sensitive) can lead to auto-cycling of the ventilator due to flow changes caused by cardiac oscillations, turbulence from condensation in the circuit, or a leak around the endotracheal tube. Even with modern ventilators, patient-ventilator synchronization remains a challenge, and mechanically ventilated children spend on average 27% of the time in conflict with their ventilator. An alternative mode of synchronization has been developed with neurally adjusted ventilatory assist (NAVA), in which the ventilator is triggered by the diaphragm electrical activity, a rapid signal of patient's breathing, leading to markedly improved patient-ventilator interactions. NAVA is not considered a conventional ventilation mode and will not be discussed further in this chapter.

12.3.4 The Control Variable: Volume-Controlled Ventilation, Pressure-Controlled Ventilation, and Pressure-Regulated Volume Control

The control variable (pressure or volume) is that parameter which is set to determine the magnitude of the tidal breath.

When volume-controlled ventilation is used, the peak inspiratory pressure (PIP) and plateau pressure (P_{Plat}) should be monitored as changes in PIP or P_{Plat} reflect changes in resistance and compliance of the respiratory system.

With volume-controlled ventilation, a specific V_T is set by the clinician and an inspiratory time is chosen. The flow provided is then integrated based on the tidal volume and inspiratory time. For example, if a V_T of 500 mL with an inspiratory time of 1 s is chosen, 500 mL will be delivered over 1 s using a gas flow of 30 L/min if flow is constant during the entire inspiratory phase (500 mL/1 s = 30 L/min). Commonly, a decelerating flow pattern is used such that the flow is higher in early inspiration and lower toward the end of inspiration. Volume-controlled ventilation may be best used in patients with relatively normal resistance and compliance of the respiratory system. The advantage of volume-controlled ventilation is that a constant V_T is delivered even with changing resistance and compliance. When volume-controlled ventilation is used, the peak inspiratory pressure (PIP) and plateau pressure (P_{Plat}) should be monitored as changes in PIP or P_{Plat} reflect changes in resistance and compliance of the respiratory system. The peak inspiratory pressure (PIP) is strongly influenced by the resistance of the tubing and of the airways. The plateau pressure better reflects the impact of ventilation on the poorly compliant lung.

To measure the plateau pressure, a no-flow end-inspiratory pause (0.2–0.5 s) should be applied to interrupt the flow and allow pressure equilibration in the absence of patient effort. Use of the plateau pressure eliminates the resistance imposed by the ETT and airways and thereby approximates the pressures that occur within the alveoli. Rising pressures require an investigation which should start at the ventilator and work toward the patient including a check for kinking of the circuit or endotracheal tube and obstruction to the endotracheal tube or major airways by mucus, auscultation to rule out mainstem intubation or bronchospasm, and a radiograph to evaluate for deteriorating alveolar disease (i.e., pneumonia, ARDS) or external factors impeding respiratory excursion (i.e., pneumothorax, restrictive diseases of the thorax, abdominal distention) or agitation. Increased resistance of the respiratory system can be suspected when observing a significant difference between peak and plateau pressures. In such cases, increasing inspiratory time decreases the inspiratory flow rate and can be used to decrease the PIP. However, the I:E ratio should be considered when increasing inspiratory times at high ventilator rates or in diseases with high expiratory resistance (asthma) because of the risk of insufficient expiratory time. In setting the ventilator rate, tidal volume, and inspiratory time (or peak flow), one must be aware of the dynamic interplay of these variables. If the peak airway pressure is unacceptably high, the pressure-controlled mode may be chosen, although a decrease in V_T may be a relatively equivalent solution.

Increased resistance of the respiratory system can be suspected when observing a significant difference between peak and plateau pressures.

With pressure-controlled ventilation, a preset pressure above PEEP is delivered over a selected inspiratory time. The inspiratory flow rate will be somewhat dependent upon the airway resistance and respiratory system compliance, achieving high levels initially and decelerating toward zero near the end of inspiration. Most ventilators allow manipulation of inspiratory gas flow rate through selection of the percentage of the inspiratory phase devoted to developing peak airway pressure (how quickly the plateau is achieved). Because inspiratory pressure is the controlled variable, changes in respiratory system mechanics (i.e., compliance and/or resistance) will result in changes in the delivered V_T and minute ventilation. During pressure-controlled ventilation, the delivered V_T is determined by the pressure level above PEEP (sometimes referred to as the delta pressure, ΔP, or the driving pressure), the inspiratory time, loss of V_T from a leak around an uncuffed ETT, and the patient's resistance and compliance. Because there is often flow cessation with pressure equilibration at the end of inspiration in pressure-controlled ventilation, the PIP is usually close to the plateau pressure. But significant differences can occur, especially when the inspiratory time is short or when the resistance of the respiratory system is high. It is usually considered that for a given minute ventilation, the mean airway pressure is higher and the peak pressure is lower in pressure-controlled than in volume-controlled mode, although this remains debated. An additional potential advantage is the decelerating flow pattern, which may help in the recruitment of alveoli with long time constants (pendelluft effect). This advantage must be balanced against the increased shearing forces of the high early inspiratory flow rates. Also, decelerating flow is now also used in most volume-controlled modes.

Given that the PIP is controlled, the risk of barotraumas is assumed to be less than with volume-controlled ventilation. Another potential advantage is that in case of deteriorating compliance, the V_T will automatically decrease for a given delta pressure, applying the principle of a more protective ventilation in the sickest patients. Pressure-controlled ventilation may be particularly beneficial in patients with decreased compliance or alveolar space disease such as pneumonia or ARDS since the higher mean airway pressure may improve oxygenation. On the other hand, the risk of large V_T is higher in pressure-controlled ventilation, as compared to a volume-controlled ventilation set with a low V_T.

During pressure-controlled ventilation, changes in respiratory system mechanics will result in changes in the delivered V_T and minute ventilation.

Pressure-controlled ventilation has also historically been preferentially used in neonates and small infant because of the lack of precision of V_T delivery by older ventilators. A discrepancy of a few mL is a significant issue when the set V_T is 20 mL. Now, critical care ventilators are relatively accurate to very small tidal volumes in neonatal modes.

As with volume-controlled ventilation, inspiratory time is set with pressure-controlled ventilation. Since most pressure modes are time cycled (end inspiration based on the inspiratory time), increasing the inspiratory time will increase the mean airway pressure. Increasing inspiratory time will increase the delivered V_T if inspiratory time is shorter than that required for all lung units to fill and come to pressure equilibration. This situation is different from volume-controlled ventilation where lengthening the inspiratory time may decrease the PIP but does not affect V_T. With pressure-controlled ventilation, the exhaled V_T should be monitored to assess ongoing changes in the compliance of the respiratory system. A decrease in the exhaled V_T should prompt a thorough investigation into its cause, which includes the same steps as outlined above for investigating an increase in PIP during volume-controlled ventilation.

The putative advantage of PRVC is that it combines the advantages of both variable controls: it delivers a relatively fixed V_T (as with volume-controlled) but with the advantageous flow pattern of pressure-controlled ventilation.

Pressure-regulated volume control (PRVC) is an option which combines features of both volume- and pressure-controlled ventilation. The tidal volume is set by the clinician, as with volume-controlled ventilation. However, the pressurization pattern follows the principle of pressure-controlled ventilation, with high early inspiratory flow rates, decelerating flow, and inspiratory pressure relatively constant during a given inspiration (square pressure-time curve). The key difference with pressure-controlled ventilation is that the level of inspiratory pressure is not set, but adjusted breath by breath by the ventilator. The ventilator continuously monitors the delivered inspired V_T and adjusts the next inspiratory pressure accordingly in order to deliver the prescribed title volume. As a safety feature, an internal software algorithm restricts the magnitude of pressure changes so that the patient cannot be markedly overinflated in response to rapid changes in compliance (e.g., tracheal tube kinking). The putative advantage of PRVC is that it combines the advantages of both variable controls: it delivers a relatively fixed V_T (as with volume-controlled) but with the advantageous flow pattern of pressure-controlled ventilation. However, the benefit of this mode has not been demonstrated in the PICU.

From the discussion thus far, it should be apparent that six basic types of ventilation can be considered: AC-pressure-controlled, AC-volume-controlled, SIMV-pressure-controlled, SIMV-volume-controlled, AC-PRVC, and SIMV-PRVC. These are the basic modes of mechanical ventilation used in the pediatric ICU today, and most modern ICU ventilators can provide all of these modes and options. Importantly, the advantages of the different options have not yet been evaluated nor compared in pediatric studies. Clinicians must decide based on the patient condition and the knowledge of the theoretical principle of these different options.

12.3.5 Supported Ventilation

Supported ventilation is defined as a breath that is triggered by the patient, assisted by the ventilator (volume or pressure), and cycled by the patient (the patient determines the inspiratory time). It is used with SIMV ventilation to support spontaneous breaths that occur in between ventilator breaths, or it can be used alone with no set minimal frequency usually as a means of weaning. In that situation, the patient determines the ventilator pattern (i.e., frequency, inspiratory, and expiratory times) by initiating and terminating each breath. Therefore, supported ventilation is used only in patients with an intact

ventilatory drive. The patient provides the work to trigger the breath, and then the remaining work for the breath is shared by the ventilator action and the patient's contribution.

In pressure support ventilation (PSV), once triggered by the patient's effort, the ventilator delivers a rapid and decelerating flow of gas to provide a preset pressure support level. The breath is terminated when inspiratory flow decreases to a percentage (generally 25%) of its peak value. At that point, the exhalation valve opens, and the circuit pressure returns to the expiratory pressure (PEEP). Therefore, the patient retains control of the cycle length and flow characteristics. The V_T is determined by the patient's inspiratory effort, the preset pressure support level, and the respiratory system impedance (resistance and compliance). Traditionally, PSV has been used to compensate for the supposed inspiratory work imposed by the ETT, but this belief has been challenged. Several studies have shown that even minimal levels of pressure support decrease excessively the work of breathing. Even though the internal diameter of pediatric ETTs is small, the flow generated through these tubes are too slow to induce important resistance. The resistance imposed by an ETT is in fact lower than the physiological resistance of the normal turbulent flow through non-intubated pediatric airways. However, PSV may help to compensate for an excessive work of breathing in a patient not yet ready for extubation.

Multiple methods of weaning ventilation with PSV have been used. One approach involves setting the pressure support level high enough to achieve delivery of the typical mechanical tidal breaths (8–10 mL/kg) with no backup SIMV rate and then gradually decrease the pressure support down till extubation criteria are met. Another method involves the combined use of SIMV and PSV in which the pressure support during assisted breaths is set to a minimal level, and the SIMV rate is gradually decreased.

In volume support ventilation (VSV), the supported breaths are triggered and cycled off in a similar way as during PSV. However, the level of pressure assist is not set but regulated by the ventilator to deliver the preset volume, provided that a maximum pressure limit is not exceeded. This mode therefore combines the theoretical benefits of PSV with the capability of providing a guaranteed minimum volume.

12.3.6 How to Set the Control Variable (Tidal Volume or Delta Pressure)

It has become increasingly clear over the last 20–30 years of mechanical ventilation that setting the mechanical ventilator to achieve "normal" values for pH and $PaCO_2$ can cause harm. While this is of utmost importance for nonhomogeneous injured lungs (e.g., ARDS), the principles extend even to those with seemingly healthy lungs. Given the discussion above on dead space ventilation, it may seem more efficient to prioritize increasing V_T to normalize pH, particularly in circumstances where alveolar dead space is increased. However, the use of supraphysiologic V_T (or pressure) has been clearly implicated in the pathogenesis of ventilator-induced lung injury, either further harming an already damaged lung or inducing injury in previously healthy lungs. While there is evidence that pediatric patients (and animals) are less sensitive to high-tidal volume ventilation than adult patients (and animals), we believe that it is still important to stay in or below the resting physiologic range of tidal volume (generally 5–8 ml/kg based on predicted body weight) and consider using lower than this (3–6 ml/kg) for children with more severe impairments in lung compliance.

Setting the mechanical ventilator to achieve "normal" values for pH and $PaCO_2$ can cause harm.

While there is some evidence that pediatric patients (and animals) are less sensitive to high-tidal volume ventilation than adult patients (and animals), it is still important to stay in or below the resting physiologic range of tidal volume (generally 5–8 ml/kg based on predicted body weight) and consider going lower than this (3–6 ml/kg) for children with more severe impairments in lung compliance.

Of course, the tidal volume cannot be decoupled from the ventilator pressures, particularly the delta pressure (peak pressure, PEEP) which is either set (in a pressure control mode) or achieved (in volume set modes). This is because the underlying disease state of the patient alters respiratory system compliance and airway resistance, which in turn affects the pressure-volume relationship. In truth, the mechanisms of injury to the lung are largely dependent on regional transpulmonary pressure gradients and regional tidal volume. The transpulmonary pressure reflects the alveolar pressure minus the pleural pressure (which may be increased if the chest wall compliance is poor), either at end exhalation or end inspiration. We can estimate the alveolar pressure using airway pressure under static conditions (no flow), both at end inspiration (plateau) and end expiration (PEEP). The pleural pressure is more difficult to measure in routine practice but can be estimated with esophageal pressure using a variety of assumptions. However, airway pressure, esophageal pressure, and V_T are estimating what is happening in the respiratory system in general. There may be marked variation in regional pressures and volumes, which ultimately may lead to lung injury.

As a general principle, peak inspiratory pressure is increased under circumstances of impaired lung compliance, impaired chest wall compliance (or increased chest wall elastance), and increased airway resistance. The risk of barotrauma and VILI is most closely tied to the transpulmonary pressure at end inspiration under static conditions, estimated by the plateau pressure minus the pleural (or esophageal) pressure and the transpulmonary driving pressure [(Pplat-P_{Es}plat) – (PEEP-P_{Es}PEEP)]. If the peak pressure is high from increases in airway resistance (such as asthma), then there will be a larger gradient between the peak and plateau pressure as the peak pressure applied during airflow is not all being transmitted to the alveoli. In contrast, if the peak pressure is high from decreased chest wall compliance (such as chest wall edema from fluid resuscitation), the plateau pressure will also be high, but some of that plateau pressure is being dissipated across the chest wall to move it out of the way. As a result, the transpulmonary driving pressure will be lower than the set ventilator driving pressure. These principles are crucial to remember when selecting pressure and volume targets for individual patients as they must be linked to the underlying respiratory system physiology. While pediatric specific evidence is weak, the general consensus is that plateau pressure should be limited to 28 cm H_2O, although there is not clear evidence for this particular target. This can be higher (up to 32 cm H_2O) if there is thought to be significant impairment in chest wall compliance (if a direct estimate of pleural pressure like esophageal manometry is not available). However, the risk of VILI is probably more closely tied to the driving pressure (plateau-PEEP), although there are no clear pediatric specific recommendations regarding optimal limits of this pressure. Adult data has advocated driving pressure targets less than 15 for clinical practice.

While pediatric specific evidence is weak, the general consensus is that plateau pressure should be limited to 28 cm H_2O, although there is not clear evidence for this particular target. This can be higher (up to 32 cm H_2O) if there is thought to be significant impairment in chest wall compliance.

Setting the optimal targets for V_T, inspiratory pressures, and ventilator rate must be individualized for patients but embrace the general principles of limiting these pressures and volumes as much as possible. This implies, particularly for patients with more severe lung disease, that normocarbia is not expected and that pH will be lower than 7.4 during the acute disease. There is no clear standard for the lower limit of "acceptable" pH, and the decisions regarding these limits need to weigh the risks of lung injury against other potential risks of low pH such as hemodynamic status and cerebral and pulmonary blood flow. This will likely mandate heavy sedation and/or muscle relaxation to suppress the patient's respiratory drive. In fact, nearly all of these recommenda-

tions regarding limiting driving, plateau pressure, and V_T are meant for the fully controlled patient. This is because when the patient is breathing spontaneously, the airway pressures underestimate the total pressure generated (sum of patient and ventilator contributions) (see section on spontaneous versus controlled ventilation).

12.3.7 How to Set the Positive End-Expiratory Pressure (PEEP)?

PEEP refers to the positive pressure applied during expiration phase until the initiation of the next breath. PEEP maintains the patency of injured lung units which may collapse during exhalation. Although physiologically accomplishing the same thing, it should be differentiated from CPAP or continuous positive airway pressure, which is the term used during spontaneous ventilation. In normal adults, the functional residual capacity (FRC, the volume at which lung recoil inward is balanced by chest wall recoil outward, obtained when no respiratory effort is ongoing and the glottis is open) and the end expiratory lung volume (EELV, the volume at which the next inspiration begins) are equal and exceed the closing capacity (CC, the lung volume at which airway closure begins to occur). Thus, spontaneously breathing healthy adolescents and adults require little PEEP to prevent atelectasis or de-recruitment. In contrast, newborns and infants younger than 1 year with their highly compliant chest wall will have an FRC that approaches and, in some cases, may be less than CC under passive (i.e., sedated or paralyzed) conditions. Infants, therefore, actively increase and maintain their EELV during spontaneous ventilation using several mechanisms: a rapid respiratory rate with short expiratory times (i.e., there is insufficient time for expiratory flows to reach zero; intrinsic or auto PEEP is present), a braking of the expiratory airflow by the laryngeal muscle contraction during exhalation (which does not occur with a tracheal tube in place) and by the persistence of diaphragm activity during expiration (tonic activity), and increased intercostal muscle tone that stabilizes the chest wall, thereby increasing elastic recoil. This active control leads to the concept of "physiologic PEEP" (typically 3–5 cm H_2O) to avoid airway closure and lung volume de-recruitment with ventilation-perfusion inequalities. Thus, sedated or intubated infants generally require the use of PEEP to overcome the loss of these dynamic compensatory mechanisms. Studies on teens and young adults demonstrated that even patients with apparently normal lungs benefit from the addition of PEEP during prolonged mechanical ventilation.

Infants actively increase and maintain their EELV during spontaneous ventilation using several mechanisms: a rapid respiratory rate with short expiratory times, a braking of the expiratory airflow by the laryngeal muscle contraction during exhalation and by the persistence of diaphragm activity during expiration, and increased intercostal muscle tone that stabilizes the chest wall, thereby increasing elastic recoil. This active control leads to the concept of "physiologic PEEP."

Higher levels of PEEP may be required in patients with alveolar space disease or other pathologic conditions that increase CC and/or decrease FRC, such as conditions associated with poor chest wall compliance (i.e., obesity, fluid overload, restrictive syndrome) or abdominal distention. Change in PEEP is frequently the first method used for regulating mean airway pressure. PEEP increases lung volume at expiration, restoring FRC and preventing the injury associated with the repetitive circle of collapse-opening-recollapse (atelectrauma). The application of PEEP also prevents airway closure during expiration, redistributes pulmonary edema fluid from alveoli to the interstitium, maintains alveolar surfactant activity, and improves ventilation to low V/Q lung units. When applied in the proper amount, PEEP should improve lung compliance so that a given change in pressure results in a greater V_T (Fig. 12.1). This positive impact of PEEP supposes an improvement in

Change in PEEP is frequently the first method used for regulating mean airway pressure.

When applied in the proper amount, PEEP should improve lung compliance.

lung aeration (prevention of lung atelectasis, reopening of non-ventilated area). However, in some patients with very severe parenchymal disease or with heterogeneous disease (complete atelectasis), the PEEP may not be sufficient to reopen the non-aerated area while being sufficient to over-distend the aerated lung segments. In these conditions, PEEP can be counterproductive and be associated with a worsening of lung compliance and of dead space ventilation. Other side effects of excessive PEEP include the depression of cardiovascular function and increase in pulmonary vascular resistance.

Several different methods of determining the optimal PEEP for patients with parenchymal lung disease have been suggested. Lung imaging (i.e., chest X-ray, tomodensitometry, lung ultrasound) can help to evaluate the expansion and aeration of the lung fields. Identification of lower and upper inflection points on the sigmoidal pressure-volume curves has also been used to determine the pressure window between overdistension and atelectasis, but it has been progressively abandoned because of its technical challenge and poor reproducibility. Titration maneuver of PEEP has been described, aiming to determine the opening pressure and the closing pressure, based on the optimal lung compliance. The monitoring of esophageal pressure may also help to determine the PEEP needed to overcome the pleural pressure during expiration, preventing the occurrence of expiratory negative transpulmonary pressure and its risk of lung segment collapse. Finally, FiO_2/PEEP grids are simple tools to guide the PEEP management based solely on the oxygenation requirements. All these methods have been studied primarily in adults, and none of them has been proven superior to simple grids. Evidence in pediatric patients is even more limited. The Pediatric Acute Lung Injury Consensus Conference (PALICC) recommended moderately elevated levels of PEEP (10–15 cm H_2O) in patients with severe PARDS, titrated to the observed oxygenation, markers of oxygen delivery, respiratory system compliance, and hemodynamic response. PEEP levels greater than 15 cm H_2O may be needed for severe PARDS although attention should be paid to limiting the plateau pressure.

Several different methods of determining the optimal PEEP for patients with parenchymal lung disease have been suggested. All these methods have mostly been studied in adults, and none of them has been proven really superior to simple PEEP/FiO_2 grids. Evidence in pediatric patients is even more limited.

The use of PEEP is also discussed in patients with serious airflow obstruction and resulting high intrinsic PEEP. In this condition, the patient's respiratory effort needs to overcome the intrinsic PEEP before inducing a pressure or flow change in the endotracheal tube, leading to marked patient-ventilator asynchrony by triggering delay or wasted efforts. The addition of PEEP in that context can improve ventilator triggering, although application of excessive levels of PEEP may dangerously increase FRC. A logical approach is to use levels of PEEP somewhat below the level of measured auto-PEEP (e.g., 80% of auto-PEEP) to facilitate triggering and to avoid increasing the already markedly elevated FRC.

12.3.8 How to Set the Respiratory Rate and Inspiratory and Expiratory Times?

The rate is commonly set primarily based on the patient's age, the desired $PaCO_2$ level, and the V_T that is delivered. In patients with severe lung injury, higher rates are frequently needed to compensate for lower V_T. In patients with less severe lung injury, higher rates and lower tidal volumes may not always be the most appropriate approach since dead space is relatively constant, causing the ratio of dead space to tidal volume (V_D/V_T) to increase as V_T is decreased. Guidelines for starting ranges of respiratory rates include 12–15 breaths/min for an adolescent, 15–20 breaths/min for an older child (6–10 years of age), 20–30 breaths/min for a toddler, and 30–40 breaths/min for a neonate. Higher rates may be needed in patients with more severe degrees of lung injury, when

hyperventilation is used to treat increased intracranial pressure or pulmonary hypertension or if endogenous CO_2 production is elevated. As previously mentioned, one may be able to limit rate since ventilation to normocapnia is frequently not required in most conditions with the permissive hypercapnia concept.

Depending on the type of ventilation (pressure-controlled or volume-controlled), the effect of changing the inspiratory time has different effects.

The setting of inspiratory time and inspiratory/expiratory ratio (I:E ratio) is frequently overlooked. Depending on the type of ventilation (i.e., pressure-controlled or volume-controlled), the effect of changing the inspiratory time has different effects. With pressure-controlled ventilation, lengthening out the inspiration time will increase the V_T in cases where the inspiratory time is shorter than that required to achieve filling of lung units with the highest time constants. More importantly, the inspiratory time along with PEEP and PIP determines the mean airway pressure. Lengthening the inspiratory time increases the mean airway pressure and will commonly increase oxygenation. Lengthening the inspiratory time can also be used as a therapeutic maneuver to help recruit alveoli with long time constants and help the resolution of atelectasis. With volume-controlled ventilation, change in inspiratory time has little impact on the V_T. Increasing inspiratory time helps to decrease the inspiratory flow rate and thereby reduce the PIP, especially in cases where airway resistance is significant. Depending on the ventilator, the inspiratory time may be set as a fixed time, by adjusting the inspiratory flow rate, as an I:E ratio, or as a percentage of the respiratory cycle. If the I:E ratio or the inspiratory percentage of the respiratory cycle is set, change in respiratory rate affects the actual inspiratory time. Since such changes could result in changes in the peak airway pressure during volume-controlled ventilation or V_T during pressure-controlled ventilation, most ventilator manufacturers have abandoned this practice. If the inspiratory time is fixed, increases in respiratory rate can result in an increase of the I:E ratio and sometimes an inverse of the I:E ratio, especially in cases of auto-triggering or when the patient has a rapid spontaneous ventilation.

During normal spontaneous ventilation, I:E ratio is 1:3 or 1:4. During conventional ventilation with AC, SIMV, or PRVC ventilation, the inspiratory time is preset during the ventilator-programmed breaths as opposed to supported breaths where the patient sets the inspiratory time. In clinical practice, the use of rate and inspiratory time is very variable. Some centers choose to use inspiratory times as low as 0.3–0.5 s for infants and up to 0.7–1 s in adolescents. Other centers commonly used lower rates and longer inspiratory times for all age groups, but it should be kept in mind that non-physiologic long inspiratory times may induce patient-ventilator asynchrony (cycling off delay), which can be uncomfortable.

The underlying disease process should also be considered. Relatively longer inspiratory times can be considered in patients with alveolar space disease and poor compliance to increase mean airway pressure and improve oxygenation. In usual practice, most clinicians restrict the inspiratory time to limit the I:E ratio at 1:1. Reversal of the I:E ratio has been used in the management of patients with severe ARDS in attempts to augment oxygenation and allow weaning of the FiO_2; however, this practice is less frequently used since the PEEP can achieve a similar results on mean airway pressure with more physiological timing. In heterogeneous lungs, prolongation of inspiration facilitates the recruitment of alveoli with long time constants (high resistance and low compliance), encourages collateral ventilation via pores of Kohn and canals of Lambert, reverses atelectasis, and improves matching of ventilation and perfusion. Importantly, the reversal of the I:E ratio may result in inadequate exhalation times, a risk that is exacerbated in case of significant spontaneous ventilation. This may result in air trapping, the stacking of one breath on another (inspira-

tion for the next breath starts before exhalation is completed), thereby resulting in auto-PEEP. An evaluation for the presence of auto-PEEP can be performed by holding the ventilator breath at the end of exhalation. When performing this maneuver, one will observe that the airway pressure will initially be equivalent to the set level of PEEP. However, when the ventilator expiratory valve closes at the end of the expiratory time, the pressure measured in the circuit will then rise above the PEEP (= auto-PEEP) because of the exhalation of the air which was "trapped" within the lung due to the insufficient length of the expiratory phase. Auto-PEEP can also be suspected when looking at the expiratory limb of the flow-time curve on the ventilator. At the end of exhalation prior to the next breath, end expiratory flow that has returned to zero generally indicates a relatively complete exhalation (i.e., absence of significant auto-PEEP).

In patients with bronchospasm and air trapping, a focus on expiratory time is important, favoring prolonged expiration to prevent air trapping. However, a common mistake is to overlook the inspiratory time in these patients with very compliant lungs but very high airflow resistance. Increased airway resistance is an inspiratory as well as an expiratory problem. Shortening inspiratory time may lead to poor distribution of inspiratory volume with failure to involve large areas of lung in gas exchange.

Most ventilators allow the addition of an end-inspiratory pause, which can be set as an absolute time or as a percentage of inspiratory time or cycle time. It can also simply be the result of the flow rate settings. The inspiratory pause holds the inspiratory volume at the end of inspiration without ongoing gas flow. This maneuver also aims to promote the recruitment of alveoli with long time constants which are secondarily filled by the air that had previously reached the alveoli with short time constants (pendelluft effect). During volume-controlled ventilation, the inspiratory pause is associated with a typical decrease on the pressure-time curve, from the peak pressure to a plateau pressure, immediately before the expiratory drop to the PEEP. During pressure-controlled ventilation, this pattern is not observed (squares pressure-time pattern), although this does not imply that the inspiratory pressure is equivalent to a plateau pressure (the flow rate is frequently not zero). To accurately measure the plateau pressure as a reflection of the lung compliance, removing the resistance component with a zero-flow condition is essential. An inspiratory hold should be manually applied (0.5 second) while the patient has no activity (i.e., deep sedation or paralysis), and the resulting pressure at the end of the pause can be recorded as the plateau pressure.

12.3.9 Balancing the Contribution of the Patient to the Ventilation: Benefit/Risk of Spontaneous Breathing

Maintaining spontaneous ventilation with diaphragm contraction in a physiologic range during the course of mechanical ventilation may prevent ventilation-induced diaphragm dysfunction (VIDD).

For the patient with respiratory failure, there is an important balance to attempt to maintain between controlled and spontaneous ventilation. With improvements in noninvasive ventilation as well as modern modes of ventilation to synchronize with the ventilator, increasingly, patients are being maintained with spontaneous ventilation. Maintaining spontaneous ventilation with diaphragm contraction in a physiologic range during the course of mechanical ventilation may prevent ventilation-induced diaphragm dysfunction (VIDD). This is crucial because diaphragm dysfunction is thought to occur in up to 40% of mechanically ventilated patients, results in more difficulty weaning from mechanical ventilation and higher rates of extubation failure, and is associated with higher post-ICU mortality. While there are several risk factors for VIDD which are related to the underlying disease state of the patient and medication choices, higher degrees of controlled ventilation, higher ventilator driv-

ing pressures, and low diaphragm contractile activity are highly implicated in VIDD. Beyond its impact on the respiratory muscles, the patient's contribution to the ventilation also has theoretical advantages for lung recruitment, for the ventilation of lung-dependent zones, for improving the ventilation-perfusion ratio, and for the sedation requirements.

On the other hand, there is increasing evidence to suggest that patients with severe lung injury can exacerbate the lung injury with spontaneous breathing, even when they are not being ventilated (patient self-induced lung injury or SILI). Hence, it may be prudent to interrupt this SILI cycle with fully controlled ventilation with lung protective strategies and sedation and neuromuscular blockade, especially in the sickest patients. Neuromuscular blockade, in particular with cisatracurium, has been shown to decrease mortality in adults with moderate to severe ARDS, with a variety of proposed mechanisms of action including prevention of SILI, relieving patient-ventilator dyssynchrony as a source of VILI, as well as modulating inflammation. These findings have yet to be reproduced in another cohort of adults with ARDS or in children. Thus, the findings should be interpreted with caution.

On the other hand, there is increasing evidence to suggest that patients with severe lung injury can exacerbate the lung injury with spontaneous breathing, even when they are not on a ventilator (patient self-induced lung injury or SILI).

Understanding this balance between controlled and spontaneous ventilation seems particularly important although a matter of debate. There are no data which reliably demonstrate if or when patients cross from "safe" to "unsafe" levels of spontaneous ventilation. It is highly possible that this balance strongly depends on the patient's illness severity. It seems logical to hypothesize that in the sickest patients, the risk of patient self-inflicted lung injury is particularly high, and its prevention should be prioritized, while in patients with less severe pulmonary disease, the benefits of maintaining the spontaneous ventilation may outweigh the risks associated with deep sedation and full ventilation control.

It is difficult to estimate the patient's contribution to mechanical ventilation when they are spontaneously breathing on a mechanical ventilator using only measures of airway pressure and flow. This is because the patient augments the change in airway pressure with a reduction in pleural pressure, resulting in a net larger transpulmonary pressure gradient to achieve the tidal volume. The delivered pressure indicated on the ventilator screen informs on the ventilator action but does not account for the patient contribution, leading to a risk of underestimation of the actual transpulmonary pressure. The use of continuous measures of esophageal pressure, as a reflection of the pleural pressure, can probably help to estimate the net total transpulmonary pressure shared between the patient and the ventilator. The utility of this monitoring is currently under evaluation. More details on esophageal pressure monitoring are provided in the monitoring section below. The patient ventilatory drive can also be estimated using the continuous recording of diaphragm electrical activity (Edi). Using a specific nasogastric tube equipped with an array of microelectrodes, some ventilators can continuously provide the level of Edi. The Edi reflects the patient ventilatory drive (not the mechanical action of the diaphragm) and is closely related to the output of the brain stem respiratory center. Edi monitoring has been primarily developed to control the ventilator, with the mode NAVA (neurally adjusted ventilatory assist). During NAVA, the ventilator support is triggered and proportional to the Edi signal. Beyond NAVA ventilation, the Edi monitoring can also be used to assess the patient ventilatory drive. Edi monitoring has demonstrated that children spend a large proportion of time with no spontaneous activity during conventional ventilation, even when they are thought to be spontaneously breathing by the clinical team.

12.3.10 Weaning the Mechanical Ventilation and Extubation Readiness Test

The course of MV begins with intubation and the provision of ventilator support. As the acute phase of the disease subsides, weaning begins which may take up 50% or more of the total time on assisted ventilation. The end of weaning is defined as the time at which the patient's spontaneous breathing alone can provide effective gas exchange. How this point can best be determined is unclear. At the end of weaning is extubation or the act of removal of the endotracheal tube (ETT). An extensive review on weaning and extubation readiness in pediatric patients was published in 2009. It described that there were many myths, unique practices, little consensus, and less objectivity surrounding these important pediatric critical care activities.

The length of weaning depends on a number of factors, among them fluid status. When total body water increases, lung compliance decreases due to increased lung water, chest wall, and diaphragm edema. In adults with acute respiratory distress syndrome (ARDS), patients managed with a conservative fluid regime had fewer MV days and a quicker return of normal lung function than those receiving a more liberal regime. The importance of fluid balance in children is not as clear although observational data in pediatric acute respiratory distress syndrome (PARDS) is also supportive of a conservative fluid approach. Positive end-expiratory pressure (PEEP) management is another factor that may affect the length of weaning. While institution and escalation of PEEP generally improves oxygenation in PARDS, pediatric practitioners are generally conservative in its application and infrequently change PEEP levels even after oxygenation improves. This may result in failure to recognize that the patient is actually ready for extubation. It is generally recommended that PEEP levels should be physiologic at the time of extubation ($\leq$ 5 cm H20) although extubation from higher PEEP levels may be important to maintain lung recruitment for certain types of patients (e.g., obesity). Sedation further complicates weaning and extubation. Oversedation may depress central respiratory drive, whereas undersedation can leave a child restless which can result in airway trauma from the ETT. Sedation assessment tools have been developed for this purpose which may be helpful to target a particular level of sedation, although implementation of a nurse-driven protocol to achieve these targets does not appear to have a significant impact on weaning times. Differences in diaphragmatic function may relate to longer weaning times in infants and young children. Accessory respiratory muscles are not as developed as in older children. As diaphragmatic dysfunction develops with prolonged MV, the duration of weaning can increase. Steroids may play a role in preventing extubation failure and reintubation by reducing tracheal inflammation associated with tracheal injuries from the ETT, as they do in another cause of subglottic edema in children, croup. Successful randomized controlled trials in both adults and children have started steroids 6–24 hours before extubation, whereas the unsuccessful ones have started the drug under 6 hours before extubation. A Cochrane Review on the role of steroids concludes, "Using corticosteroids to prevent (or treat) stridor after extubation has not proven effective for neonates, children or adults. However, given the consistent trend toward benefit, this intervention does merit further study." Finally, other factors are likely important to the weaning process, but there is a dearth of research in these areas, and they are not further discussed. These include cardiac function, postoperative, neurologic, and nutritional status.

Predictive Indices for Weaning. Several indices have been developed to predict success in weaning and extubation. Although these indices have been vari-

ably used in research, they have not found common use in clinical care, some because of their complexity and others due to lack of proven benefit over clinical judgment in pediatric practice.

Rapid Shallow Breathing Index (RSBI = f / V_T). The RSBI was devised by Yang and Tobin and found to be a good discriminator of weaning success and failure in adults. This test has become more widely used in adult practice and research with varying success. Some investigators have demonstrated that RSBI normalized to actual body weight (f/V_T (ml/kg)) has some predictive ability in pediatrics, although these values are often very low by the time extubation readiness testing occurs, reinforcing the concept that these should be used early in the course of weaning. Both an RSBI <8 or <11 breaths/min/mL/kg body weight have been promoted as good predictors of successful extubation.

Compliance, Respiratory Rate, Oxygenation, Pressure Index (CROP Index) [Dynamic Compliance × (PaO_2/PAO_2) × Maximal Negative Inspiratory Pressure) / Respiratory Rate]. In pediatrics, a CROP Index of >0.15 or >0.1 mL/kg body weight/breaths/min have been recommended as good predictors of successful extubation.

For both RSBI and CROP, as with adults, conflicting studies found that those indices did not reliably predict extubation outcome in children. The RSBI has become moderately popular in adult ICUs. However, since there is a wide range of age groups with different respiratory rates, it may not be a good predictor of extubation success or failure in the pediatric population. Whether age-specific f/V_T ratios would perform better is currently unknown.

Volumetric Capnography. The slope of an expired, single-breath CO2 waveform can be used to calculate the physiologic dead space (V_D/V_T) and a value <0.50 reliably predicted extubation success, whereas a V_D/V_T > 0.65 identified patients at risk for failure. Not all investigators have been able to reproduce this. Volumetric capnography requires an arterial or a capillary blood gas, and the predictive ability may depend on the types of patients studied, degree of parenchymal lung disease, and tidal volume generated.

The slope of an expired, single-breath CO_2 waveform can be used to calculate the physiologic dead space (V_D/V_T) and a value <0.50 reliably predicted extubation success, whereas a V_D/V_T > 0.65 identified patients at risk for failure.

12.3.10.1 Techniques of Weaning

Not all patients require gradual weaning.

Not all patients require gradual weaning. Both adult and pediatric studies have shown that when patients pass a spontaneous breathing test (SBT) and are subjected to an extubation readiness test (ERT), 50–75% of the patients are deemed ready to extubate and will do so successfully. Standardized weaning protocols have been promoted to minimize the time on a ventilator and provide uniform decisions about weaning. The concept of ventilator-free days as an end point is implicitly based on having a low failed extubation rate for any reason other than the original cause of respiratory failure. This standard may be inappropriate in pediatric trials since there is not only a higher rate of failed extubation in this group, but up to 40% of failures may involve upper airway obstruction (UAO). For research purposes, it may be important to define the end of successful weaning in a manner short of extubation. Overall, it is likely that a consistent approach to ventilator weaning will shorten ventilator time and result in better outcomes.

The most common approach to weaning infants and children is gradual reduction of ventilator support. Weaning with synchronized IMV (SIMV) occurs by reducing the ventilator rate. With pressure support ventilation (PSV alone or in combination with SIMV), the inspiratory pressure is initially set to provide the required support and then reduced gradually. As mentioned above, volume support ventilation (VSV) is a special form of PSV that targets a specified minimal tidal volume. Weaning with VSV is somewhat automatic in that the support level required to maintain the set tidal volume is reduced auto-

matically as respiratory mechanics improve. Its disadvantage is it may allow the patient to work harder than desired. Extubation occurs from a low level of ventilator support or after an extubation readiness test (ERT). It appears that it is common practice to extubate infants and children from a low level of ventilator support though there is no rationale for this.

A second school of thought recommends to continuously provide the ventilator support to rest the patient's respiratory muscles and to perform a daily extubation readiness test. MV is discontinued if the test is passed. This approach has been more commonly used to wean adult patients than children.

In a small number of patients, weaning is attempted with alternating periods of complete ventilator support and graded spontaneous breathing with assistance. This "sprinting" is performed on the theory that the respiratory muscles can be slowly trained to sustain complete spontaneous breathing. There is currently little evidence that such an approach is an effective way of training muscles. There are also no data comparing such an approach with more traditional approaches of weaning. A multicenter randomized controlled trial comparing three modes of weaning found that there were no significant differences between having no protocol and weaning by PSV or VSV.

12.3.10.2 Criteria for Readiness for Extubation

Readiness for extubation implies that weaning is completed, and the patient is sufficiently awake with intact airway reflexes, is hemodynamically stable, and has manageable secretions.

Readiness for extubation implies that weaning is completed and the patient is sufficiently awake with intact airway reflexes, is hemodynamically stable, and has manageable secretions. Extubation failure has been variably defined as reintubation within 24–72 hours. Tests commonly used to assess extubation readiness include testing for a leak around the ETT ("leak test") and assessing respiratory muscle strength by measuring negative inspiratory force (NIF).

Cuffed ETTs have been cited as a cause of increased UAO on extubation, but several studies have found no difference in the incidence of failed extubation over all age groups between those intubated with appropriately sized cuffed or uncuffed tubes. The leak test whereby air is heard (without using a stethoscope) to leak around the ETT at low pressure, usually <20–25 cm H_2O, is commonly used to predict UAO after extubation. However, it is neither a sensitive nor specific test. For cuffed ETTs, cuff leak fraction is calculated as (expiratory tidal volume with cuff inflated minus expiratory tidal volume with cuff deflated)/(expiratory tidal volume with cuff inflated). Evaluating uncuffed ETTs, leak percentage is calculated as the fraction (inspiratory tidal volume minus expiratory tidal volume)/(inspiratory tidal volume). In a study of 409 infants and children immediately prior to their extubation, it was found that a cuff leak fraction less than 10% or a leak pressure (with the cuff deflated) greater than 25 cm H_2O was highly associated with risk of UAO following extubation. The presence or absence of a leak was not associated with UAO for uncuffed ETT.

Negative Inspiratory Force (NIF). In the PICU, the test is usually performed quickly at the bedside with an uncalibrated manometer and with both inspiration and exhalation obstructed. The test has not been hitherto standardized nor validated in children. Nonetheless, it is reassuring if a spontaneously breathing patient has a routinely obtained NIF of at least 30 cm H_2O. Similarly, consistently low values (i.e., below 15 cm H_2O), irrespective of technique, are unlikely to be associated with successful weaning to extubation.

12.3.10.3 Impact of Endotracheal Tubes on Weaning and Spontaneous Breathing Trials

No matter how small the ETT, effort of breathing on CPAP of 5 cm H_2O best estimates post-extubation work.

Many clinicians believe that, for an infant or young child, breathing through a small ETT is akin to breathing through a straw, thereby imposing an unacceptable work of breathing. It is therefore a frequent practice to extubate children from levels of 5–10 cm H_2O PSV above PEEP in order to overcome the presumed increased effort of breathing. This notion is contrary to both clinical observation and physiology. In a large prospective trial, the pressure rate product (PRP) was measured in infants and children during preparation for extubation. PRP has been validated as a surrogate for work of breathing and is defined as respiratory rate times peak-to-trough esophageal pressure. The PRP was recorded on PSV and CPAP prior to and after extubation. No matter how small the ETT (down to 3.0 mm ID), effort of breathing on CPAP of 5 cm H_2O best estimated post-extubation work. Furthermore, the PRP on PSV was almost half the level after extubation, significantly underestimating the post-extubation effort of breathing. The reasonable conclusion from this study is that, all things being equal, if a patient cannot breathe comfortably on CPAP alone, there is little chance he or she will do so when extubated.

A further benefit of PRP is that when evaluated along with the maximum NIF, the combination of the former being >500 and the latter ≤30 cm H_2O predicts high reintubation rates of >20%. These values reflect diminished respiratory muscle strength (aPImax) in the face of high effort of breathing (PRP).

12.3.10.4 Assessment of Post-extubation UAO

Upper airway obstruction (UAO) is frequent after endotracheal extubation. Definitive data on risk factors and prevention of pediatric post-extubation UAO have been lacking. More objective measures of post-extubation UAO severity in infants and children may help identify risk factors and elucidate optimal treatment or prevention strategies. Inspiratory flow limitation is relatively specific to extrathoracic UAO, characterized by disproportionately large inspiratory effort relative to flow. The most widely accepted method to measure flow is spirometry, which, for noncooperative spontaneously breathing children, requires a tight-fitting mask over the nose and mouth. This may require sedation and results in changed flow dynamics. Respiratory inductance plethysmography (RIP) is a less invasive alternative to spirometry. With RIP, variations in the self-inductance of a coil (wires around the rib cage (RC) and abdomen (ABD)) are measured as a result of changes in the cross-sectional area of the RC and ABD. The combination of calibrated RIP and esophageal manometry has shown promise for providing both an objective measure of the severity of post-extubation UAO and also some insights into risk factors for UAO. With the addition of a pneumotachygraph on the ETT prior to extubation, RIP flow can be calibrated during 3–5 breaths of airway occlusion during an NIF procedure. This allows the construction of noninvasive flow-pressure loops from the RIP and esophageal pressure measurements (◘ Fig. 12.3).

These loops can be inspected for inspiratory flow limitation after extubation to characterize post-extubation UAO. Patients can be observed as having UAO when inspiratory flow limitation is newly observed after extubation with an increase in PRP (◘ Fig. 12.4, panel A). The reversal of inspiratory flow limitation can also be seen after the child receives a UAO-specific intervention such as racemic epinephrine, heliox, or corticosteroids. UAO can be further classified as subglottic if a jaw thrust maneuver does not reduce PRP by at least 50%.

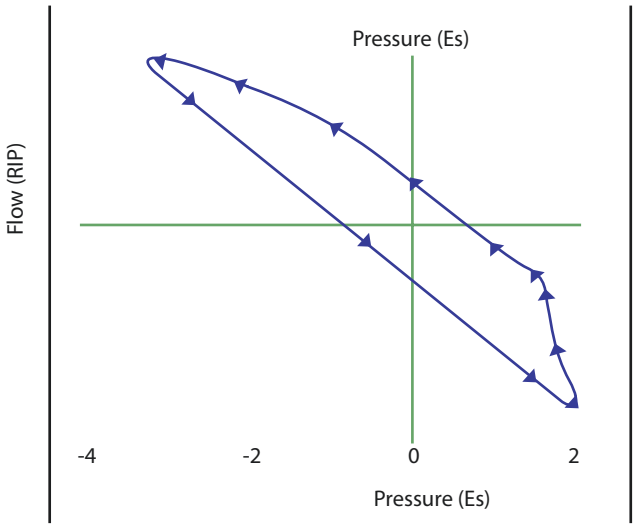

Fig. 12.3 Flow-pressure loop displaying the evolution of flow, obtained from calibrated RIP belts around the thorax and abdomen, and esophageal pressure, obtained using an esophageal balloon catheter

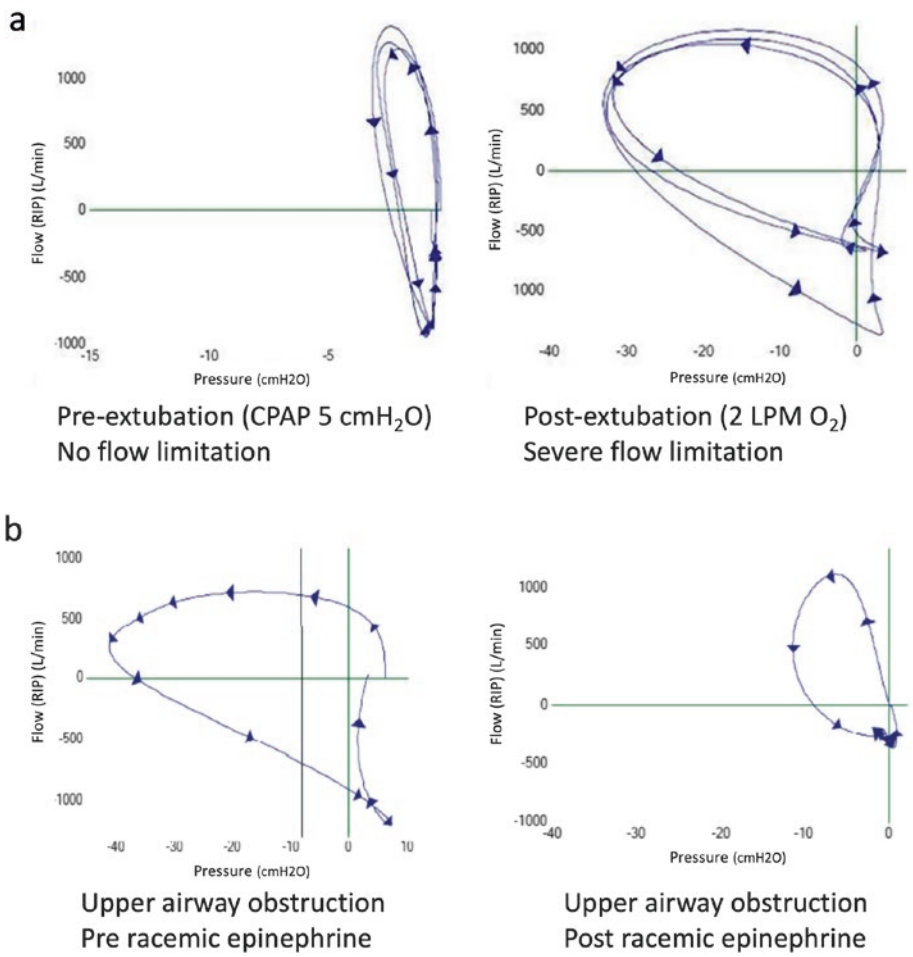

Fig. 12.4 Panel A illustrates the evolution of the flow-pressure loop as recorded in Fig. 12.3 in a 6-month-old infant before (left) and after extubation (right). The right panel shows inspiratory flow limitation after extubation due to upper airway obstruction, as denoted by the flattened flow-pressure limb above the X-axis and large negative change in esophageal pressure. The pressure rate product also increased tenfold. Panel B illustrates the evolution of inspiratory flow limitation in an infant with UAO before (left) and after racemic epinephrine (right). The narrowing of the loops illustrates the improvement in UAO

12.3.11 Role of Automation and Clinical Decision Support System

While the basic principles of lung protective ventilation have been embraced by pediatric intensive care physicians, there is still great variability in ventilator management.

While the basic principles of *lung protective ventilation* have been embraced by pediatric intensive care physicians, there is still great variability in ventilator management. Most critical care practitioners believe they are being lung protective, but it is likely that consistent, replicable decisions are not made to minimize ventilator support across the duration of mechanical ventilation for patients with lung injury. Since respiratory support is required in the majority of children in the PICU and because complications may occur with its use, it is essential to develop strategies to improve patient outcome and reduce medical errors related to mechanical ventilation. The observed variation in clinical practice is likely due in part to clinicians' low adherence to guidelines, and this is compounded because many facets of caring for a mechanically ventilated patient in the PICU lack high levels of evidence or evidence is conflicting. There is good evidence, however, that clinical decision-making with a protocol decreases practice variation between clinicians, standardizes patient care, and improves research and patient outcomes. Replicable ventilator management decisions should help decrease practice variability and directly shorten the length of mechanical ventilation for children in pediatric ICUs. A Cochrane systematic review assessing the impact of automated versus nonautomated weaning for critically ill adults and children identified 21 trials, and the meta-analysis suggested a reduction in ventilation duration and ICU length of stay, although a great heterogeneity was observed, and only two trials were conducted in pediatric ICU.

Decision support tools, both paper and electronic, have been demonstrated to improve medical care, reduce errors, and improve patient outcomes. However, paper-based protocols are dependent on caregiver availability and are often written in broad terms so they remain dependent on clinician judgment and local context for interpretation and therefore are difficult to transfer from one PICU or NICU to another intensive care unit. Paper-based tools can be difficult to follow accurately, leading to low adherence rates. Computer decision support (CDS) tools like computer-based protocols are an automated method to reduce medical errors. Such tools aim to ensure replicable, evidence-based clinician decisions for equivalent patient states and to improve protocol compliance. The tools can generate explicit recommendations that can be carried out with little inter-clinician variability while still remaining responsive to the patient's unique situation. The tools can assist clinicians by standardizing descriptors and procedures, by consistently performing calculations, by incorporating complex rules with patient data, and by capturing data relevant to decision-making. Computer-based protocols can contain more extensive detail than textual guidelines or paper-based flow diagrams while at the same time protecting the user from complexity and information overload.

Decision support tools vary in terms of how dynamic they are, the degree of specificity of their recommendations, and the level of integration into workflow. One end of the spectrum includes general guidelines that consist of a set of broad, static recommendations. At the other end of the spectrum are computerized protocols, which function as a set of standardized orders, with detailed explicit instructions based on dynamic patient-specific parameters, available at the point of care. The latter type of protocol has been called an "explicit computerized protocol" (ECP). A few ventilators have incorporated closed-loop algorithms to automatically adjust the ventilator settings depending on the patient condition and trajectory. These specific modes have been mostly developed for the weaning phase of the ventilation (e.g., SmartCare

system), and more recent tools aim to manage the complete ventilation process from the acute to the weaning phase (e.g., Intellivent system).

The systems need to be fed with clinical information and ventilator data. The first parameter to be defined is a surrogate of the child's lung volume. Actual body weight is not accurate enough as children may be malnourished or obese. The PALICC guidelines recommend using predicted body weight. Height is a better alternative in most cases except when neuromuscular weakness or spinal deformity is present. In such circumstances, ulna length is an excellent surrogate. Ventilator input data may include set ventilator parameters and measured ventilator parameters (i.e., spontaneous respiratory rate, expiratory tidal volume and air leak around the endotracheal tube, dynamic compliance, resistance). CO_2 removal is assessed intermittently by arterial or capillary PCO_2 on blood gas, continuously with end-tidal CO_2 ($PETCO_2$) and transcutaneous PCO_2 and also indirectly by spontaneous respiratory rate and tidal volume in some assist modes when respiratory control is functioning properly. Oxygenation can be assessed intermittently by PaO_2 on blood gases and continuously by SpO_2. For real-time adjustment of ventilation, ECPs are currently using SpO_2 and end-tidal CO_2 in addition to respiratory rate and tidal volume or predicting PaO_2/FiO_2 ratio from SpO_2/FiO_2 ratio and pH from a previous arterial to end-tidal CO_2 difference utilizing the Henderson-Hasselbalch equation.

Barriers to protocol use are considerable including lack of awareness, lack of familiarity with the protocol, lack of agreement, lack of efficacy, lack of known improved outcome, and lack of ability to overcome the inertia of previous practice. There are also external barriers: protocol-related barriers (i.e., not easy to use, not convenient, cumbersome, confusing) and environment-related barriers (e.g., new resources or facilities not accessible). To ensure acceptance, users must feel that they can count on the system to be available whenever they need it. The amount of downtime needed for data backup, troubleshooting, and upgrading should be minimal. The response time must be fast, data integrity must be maintained, and data redundancy must be minimized. It is also important to assess the amount of training necessary for users to feel comfortable with the system. The ventilator market itself is also a barrier to the implementation of ECPs. There are numerous companies, and the competition between them results in difficulties implementing the same ECP in different ventilators.

12.3.12 Monitoring of the Mechanical Ventilation

12.3.12.1 Blood Gas

Noninvasive SpO_2-based oxygenation saturation index (OSI) (mean airway pressure x FiO_2/SpO_2 x 100) is an adequate surrogate marker for the ABG-based oxygenation index OI (mean airway pressure x FiO_2/PaO_2 x 100), as long as SpO_2 is between 80% and 97%.

While arterial blood gas (ABG) and capillary blood gas (CBG) measurements are the standards for supportive management in pediatric intensive care units, frequent use of SpO_2 (and end-tidal CO_2) requires incorporating noninvasive technologies into decision-making and scoring systems. Given the challenges to placing arterial catheters in small children in daily care, practitioners frequently make decisions for children based on oxygen saturations obtained from pulse oximetry. Pulse oximeters are developed to perform optimally in a range of oxyhemoglobin saturation from 70% to 100%. It is not always clear how well pulse oximeters perform when the majority of observations are in infants and children in a hypoxemic range. Nonetheless, in practice, pulse oximetry in the low range is now routinely used for clinical decision-making for children with cyanotic congenital heart disease.

ABG-based measures of hypoxemia such as PaO_2/FiO_2 (PF) ratio have been used in ICU severity of illness scores as diagnostic criteria for acute respiratory distress syndrome (ARDS) and for scoring of lung injury. It is now well demonstrated that noninvasive SpO_2-based oxygenation saturation index OSI (mean

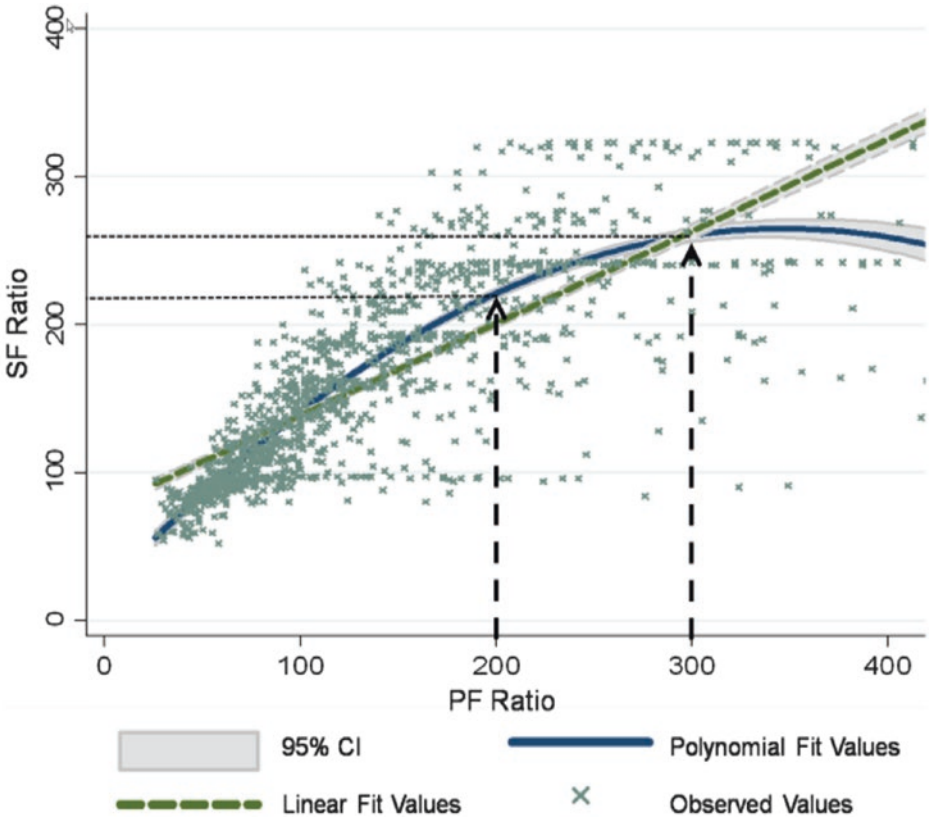

Fig. 12.5 Association between the PaO_2/FiO_2 (PF) ratio and the SpO_2/FiO_2 (SF) ratio in a cohort of children with hypoxemic respiratory failure and a SpO_2 between 80% and 97%

airway pressure × FiO_2/SpO_2 × 100) is an adequate surrogate marker for the ABG-based oxygenation index OI (mean airway pressure × FiO_2/PaO_2 × 100), as long as SpO_2 is between 80% and 97%. Similarly, the S/F ratios of 264 and 221 correspond well with the P/F ratio cutoff values of 300 and 200, respectively (Fig. 12.5). While it is clear that there is considerable scatter of SpO_2 values corresponding to a PaO_2 value, the accuracy of these measurements can be improved if targets of SpO_2 are consistently between 88% and 95%.

The most widely used noninvasive sensor to estimate adequacy of ventilation is end-tidal carbon dioxide pressure ($PETCO_2$). However, the relationship between $PETCO_2$ and $PaCO_2$ changes as a function of alveolar dead space. Additionally, estimating pH from $PETCO_2$ is confounded by changing metabolic acidosis with illness frequently compounded by the use of diuretics. Nonetheless, incorporating noninvasive measures of intrapulmonary shunt, noninvasive continuously available values from the ventilator and previously known values for pH and PCO_2 from an ABG or CBG, allows accurate pH prediction for up to 12 hours in a relatively stable patient, as illustrated in Fig. 12.6. The advantage of continuous pH projection is that it permits more frequent (lung protective) ventilator changes than from intermittent blood gases. Similarly, a model has been developed to continuously estimate the $PaCO_2$ based on the $PETCO_2$, mean airway pressure, FiO2, and the capnographic index (KPIv) derived from volumetric capnography, using the following equation:

$$\text{Predicted } PaCO_2\,(\text{mmHg}) = 0.859 + 0.827 \times PETCO_2\,(\text{mmHg}) + 0.310 \times MAP\,(\text{cm}\,H_2O) + 0.081 \times FiO_2\,(\%) + 0.529 \times \text{KPIv}$$

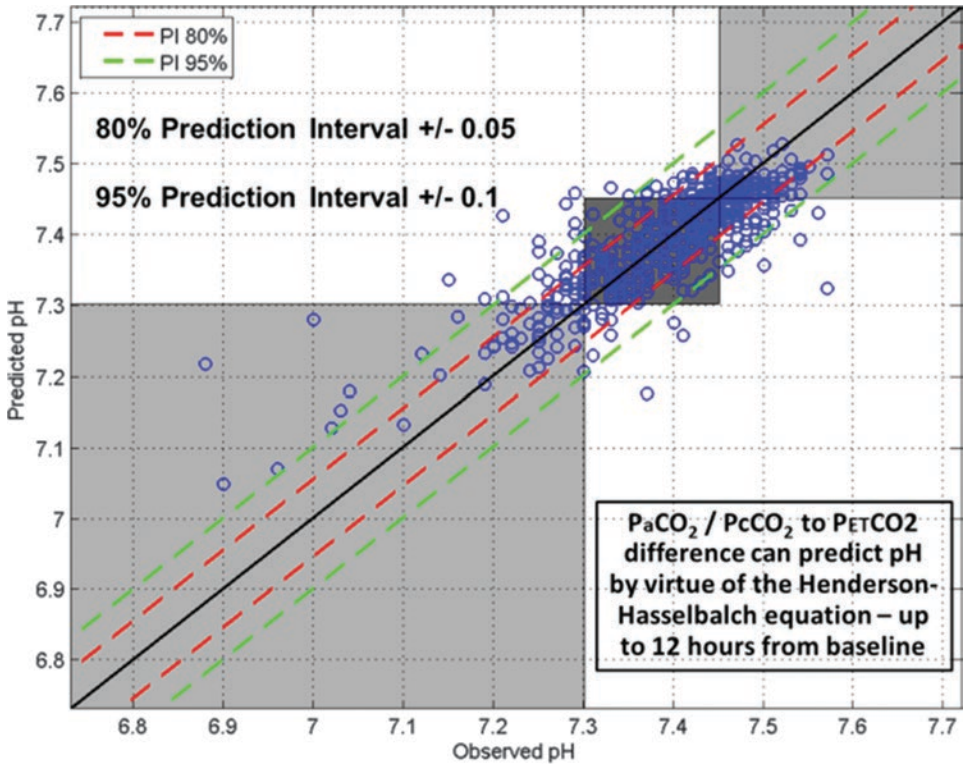

Fig. 12.6 pH prediction utilizing the Henderson-Hasselbalch equation, based on the previous pH and the PCO_2-$PETCO_2$ difference

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This model is shown to achieve a predicted $PaCO_2$ correct at ±5 mm Hg in 95% of measurements.

12.3.12.2 Capnography

Capnography describes the continuous display of carbon dioxide partial pressure in the expired breath ($PETCO_2$). Capnography is noninvasive, accurate, easy to do, and relatively inexpensive and has been studied extensively. Capnography can be measured with the mainstream technique (i.e., sensor placed in line between the proximal end of ETT and ventilator circuit Y-piece) or with the sidestream technique (exhaled gases are aspirated from near the proximal end of the endotracheal tube and analyzed at a sensor nearby). There are two distinct types of capnography. Conventional, time-based capnography allows only qualitative and semiquantitative measurements. Volumetric (volume-based) capnography has emerged as the preferred method to assess the quality and quantity of ventilation. Volumetric capnography combines the measurement of exhaled CO_2 with continuous flow (and hence volume) measurement to provide a continuous measure and visual display of the quantity of CO_2 eliminated and how it relates to expired breath volume. These measurements can be used to estimate anatomic and physiologic dead spaces and ventilation effectiveness, while with both methods, pattern recognition of displayed waveforms can be used to identify pathophysiological problems, as detailed in Fig. 12.7. In the figure, the area X represents the actual volume of CO_2 exhaled at one breath. Adding all single breaths at 1 minute gives the total elimination of CO_2 per minute ($V'CO_2$). Area Y represents the amount of CO_2 that is not eliminated due to alveolar dead space. The latter is increased in cases of lung overdistention, pulmonary embolism, pulmonary hypertension, and decreased cardiac output. It decreases when these conditions are ameliorated. An elevation of the baseline during Phase I indicates rebreathing of

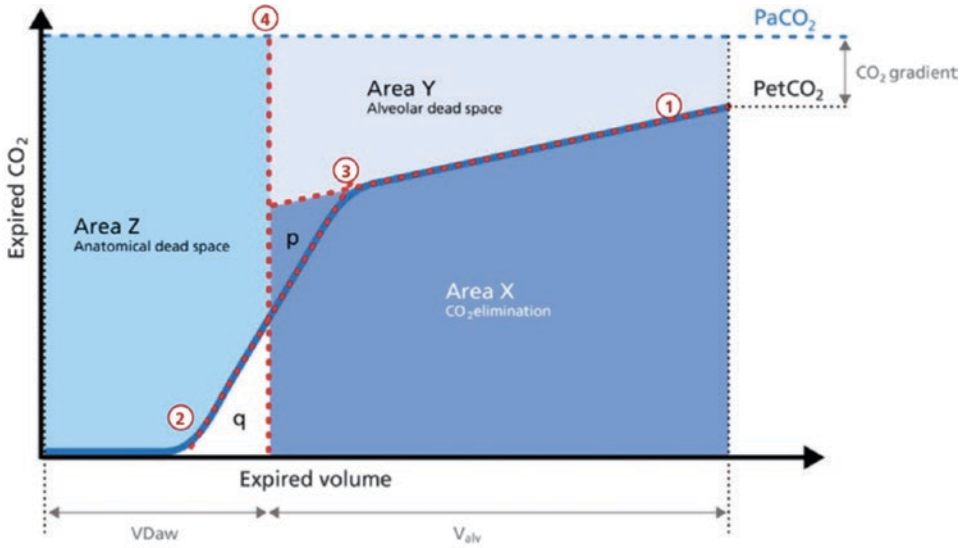

Fig. 12.7 Volumetric capnography typical tracing and identification of the different slopes and corresponding physiological variables, where (1) signifies the slope of Phase III, (2) signifies slope of Phase II, (3) the intersection of lines 1 and 2 define the limit between Phases II and III, and (4) a perpendicular line is projected onto the X-axis, and its position is adjusted until the areas p and q on both sides become equal

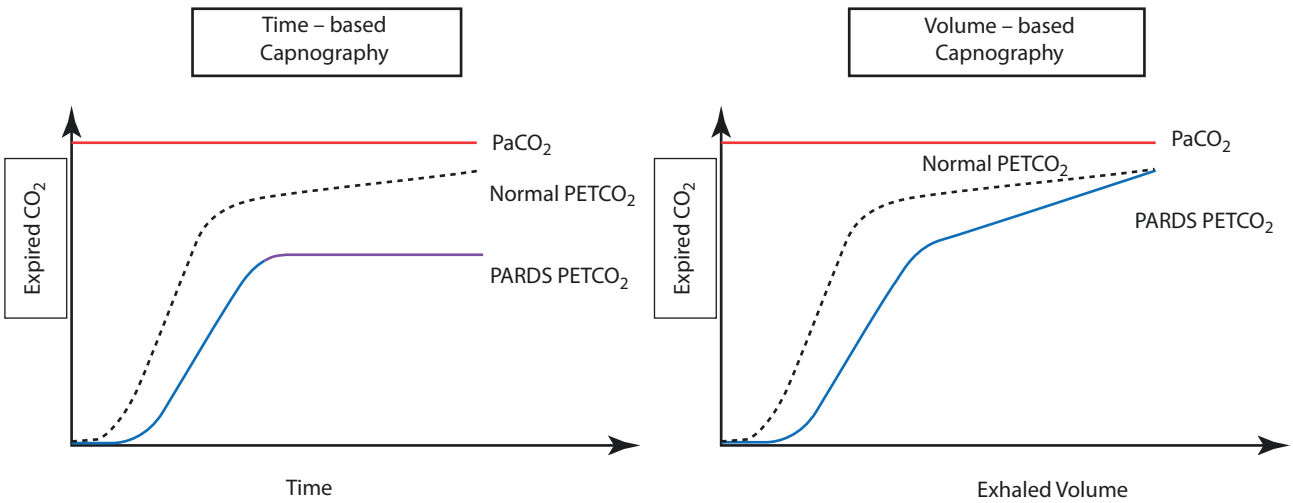

Fig. 12.8 Schematic representation of time-based capnography (left panel) and volumetric capnography (right panel) in patients with pediatric acute respiratory distress syndrome (PARDS)

CO_2, which may be due to mechanical problems with the ventilator, the need for recalibration of the CO_2 sensor, or incomplete reversal of neuromuscular blockade while breathing spontaneously.

In pediatric ARDS, the ventilation-perfusion ratio is disturbed, and both types of capnography have been associated with mortality prediction, particularly when added to oxygenation metrics. Using time-based capnography, the alveolar dead space will be increased, but the slope of Phase III is usually almost flat. More distinct changes are shown by the volumetric capnography curve. Here, Phase I may be larger due to increased anatomic dead space caused by PEEP. The slope of Phase II is decreased due to lung perfusion abnormalities, and the slope of Phase III is increased due to lung heterogeneity (Fig. 12.8).

Capnography can be used to estimate anatomic and physiologic dead spaces and ventilation effectiveness.

12.3.13 Pleural Pressure Monitoring

The pleural pressure estimate may be useful for setting the PEEP, setting the delta pressure, and estimating patient effort and degree of spontaneous ventilation.

As mentioned above (sections on setting inspiratory pressure and PEEP), an estimate of pleural pressure has many theoretical implications during mechanical ventilation. Unfortunately, pleural pressure cannot be measured in routine clinical practice, so the most common surrogate relies upon an esophageal pressure. In general, the esophageal pressure is measured in the lower 2/3 of the esophagus and presents a global estimate of the pleural pressure in the thorax. In truth, regional pressure may be considerably different since during normal physiologic conditions, the pleural pressure differs from apex to base of the lung or from ventral to dorsal regions when the patient is lying supine. The pleural pressure estimate may be useful for setting the PEEP, setting the delta pressure, and estimating patient effort and degree of spontaneous ventilation. It may also be useful to quantify patient-ventilator asynchrony and measure intrinsic PEEP and a variety of other applications.

During fully controlled ventilation (i.e., no spontaneous effort), the pleural pressure is used to estimate transpulmonary pressure at end expiration (to set PEEP) and at end inspiration (to set tidal volume or delta pressure). At end expiration, when there is no airflow (expiratory hold), the pressure in the pleural space gives an estimate of the pressure being exerted by the chest wall. Under normal conditions (not mechanical ventilation), the pleural pressure is slightly more negative than the alveolar pressure (i.e., −3 to −5 with alveolar pressure = 0). This results in a slightly positive transpulmonary pressure (Palv-Ppl of +3 to +5) at end expiration, which promotes the alveoli staying open, above the critical closing capacity. If the pleural pressure is increased (i.e., obesity, chest wall edema), then the transpulmonary pressure at end exhalation will become negative, without applying PEEP. This may promote alveolar collapse and can exacerbate atelectrauma as a mechanism of lung injury, particularly for patients with ARDS. Hence, an area of active investigation is to determine whether using esophageal manometry (generally with esophageal balloon catheters) as an estimate of pleural pressure can be used to select optimal PEEP levels in patients with ARDS. A Phase II study has shown some promise in this approach for adults with ARDS compared to the ARDSnet low PEEP/FiO_2 grid. A larger Phase III study recently studied the titration of PEEP with esophageal pressure compared to the ARDSnet high PEEP/FiO_2 grid, in adults with severe ARDS. In this study, there was no difference. While this approach likely has applicability in pediatrics, there are additional limitations with the accuracy of esophageal balloon catheters in small children, which would be important to overcome before widespread use.

The esophageal pressure can be used at end inspiration (during an inspiratory hold) to estimate the transpulmonary driving pressure and transpulmonary pressure at plateau. These variables may be crucially important when considering VILI from barotrauma. This is because under conditions of significant chest wall restriction, much of the inspiratory pressure is dissipated across the chest wall. Having a more precise estimate of the transpulmonary pressure may allow for slightly higher plateau and driving pressures to be applied, in circumstances where the chest wall compliance is poor. This remains an active area of investigation, with limited current evidence to suggest a particular target for this transpulmonary pressure. Similar issues with the accuracy of balloon catheters in pediatrics need to be overcome before this approach can be considered for widespread use in children.

Applications related to selection of PEEP and driving pressure using esophageal pressure are highly sensitive to the accuracy of the balloon catheter because an accurate assessment of the actual pleural pressure is needed to set the airway pressure. In contrast, applications related to effort or work of

breathing are more robust in pediatrics using esophageal manometry because they simply use the change in esophageal pressure rather than the absolute value for applications. Classically, esophageal manometry has been combined with measures of tidal volume, airway pressure, and flow to measure work of breathing. This work of breathing is characterized by the force needed (i.e., change in pressure, both airway and esophageal) over a distance (i.e., the tidal volume). This work is shared between the patient and the ventilator, with an algorithm used to divide the contribution coming from the patient with what is coming from the ventilator, based on the Campbell diagram. This has advantages of understanding the overall stress on the respiratory system (in this case, shared between patient and ventilator). However, oftentimes, the patient's effort while on mechanical ventilation is the more important clinical variable to consider when adjusting the ventilator settings. This is frequently estimated with the pressure time product (PTP), given by the area under the esophageal pressure tracing during inspiration times the respiratory rate, where inspiration is typically defined using spirometry to characterize when airflow crosses zero. Therefore, this requires the use of an additional sensor (other than esophageal manometry) to estimate patient effort of breathing. To overcome this limitation, some investigators use the pressure rate product (PRP), which is defined as the peak-to-trough change in esophageal pressure during a breath multiplied by the respiratory rate. This is simpler to calculate and does not require an additional sensor. While these metrics generally provide similar results under conditions of increased respiratory load, the circumstances of when to use one versus the other remains an area of investigation.

12.3.14 Chest Radiography

A chest radiography is generally obtained after tracheal intubation and, in most situations of clinical deterioration, to detect complications or the displacement of tubes and catheters. It is also required to establish the diagnosis of PARDS, even if its interpretation is difficult with large interobserver variability. The optimal frequency of radiograph control in mechanically ventilated children is not established. Some studies conducted in adult ICUs suggest that an on-demand strategy can safely replace the routine daily radiograph strategy. It is not certain if this approach may be completely transposable to children with acute respiratory failure, in whom half of routine chest X-rays are followed by an intervention. However, routine radiography could probably be avoided when the risk of intervention is low, in particular when the number of devices is low, and in stable and older children.

12.3.15 Diaphragm Ultrasound

In recent years, diaphragm ultrasound has become an increasingly utilized modality in research and clinical practice to quantify patient effort of breathing as well as identify architectural changes in the diaphragm which may signify ventilator-induced diaphragm dysfunction. There are a variety of approaches which advocate slightly different methods for the orientation of the ultrasound probe and methods for measurement. The general concept is to measure the diaphragm in the zone of apposition, where it is running near vertically along the chest wall. Serial measurement of the diaphragm thickness during exhalation can be used to identify atrophy of the muscle throughout the course of ventilation and is thought to be an indirect surrogate for VIDD. Further investigation is needed to see if these architectural

Very low diaphragm thickening fractions have been described as common during controlled ventilation and may be implicated in thinning of the diaphragm during MV. In contrast, very high thickening fractions may be present when work of breathing is high and has been associated with hypertrophy of the diaphragm muscle, which also may have implications on overall diaphragm function.

changes truly correspond to direct measures of respiratory muscle strength (such as airway or esophageal pressures during airway occlusion (i.e., aPiMax or ePiMax). In addition, similar measurement of the diaphragm thickness and how this varies during inspiration compared to exhalation can be used to estimate a thickening fraction (or diaphragm contractile activity). Very low thickening fractions have been described as common during controlled ventilation and may be implicated in thinning of the diaphragm during MV. In contrast, very high thickening fractions may be present when work of breathing is high and has been associated with hypertrophy of the diaphragm muscle, which also may have implications on overall diaphragm function. As of now, these tools fit largely in the research domain in pediatric mechanical ventilation.

12.3.16 Diaphragm Electrical Activity Monitoring

The monitoring of electrical activity of the diaphragm (Edi) is a new, minimally invasive, bedside technology that was primarily developed for ventilation mode NAVA. In addition to its role in NAVA ventilation, this technology provides the clinician with previously unavailable and essential information on diaphragm activity. The Edi signal is acquired using a specific nasogastric catheter equipped with multiple microelectrodes, connected to a specific ventilator, in which a signal processing algorithm allows the detection of the diaphragm position and the construction of an optimal Edi signal not affected by the diaphragm movement. The Edi is a rapid electrical signal, which closely reflects the output of the phrenic nerves. The quantification of the Edi allows easy detection of overassistance or oversedation with absent ventilator drive. This situation occurs frequently during conventional ventilation. Approximately one-third of children had no or very low diaphragm activity in a recent study. Increased inspiratory Edi levels can also suggest insufficient support, while a strong tonic activity may reflect the patient's efforts to increase lung volume. Edi monitoring also allows the detection and quantification of patient-ventilator asynchrony, which occurs during more than a quarter of the time during pediatric conventional ventilation.

Importantly, Edi reflects the ventilatory drive (i.e., patient "demand"). When correlated to the resultant mechanical action (e.g., the inspiratory force generated by the diaphragm contraction, with no ventilator support), one can obtain an index of the neuromechanical efficiency (NME) of the diaphragm.

$$\text{NME} = \text{negative inspiratory pressure} / \text{inspiratory Edi}$$

The quantification of the Edi allows to easily detect situations of overassistance or oversedation with absent ventilatory drive, insufficient support with high drive, and asynchrony.

The combination of Edi with esophageal pressure monitoring provides an estimate of respiratory neuromechanical efficiency.

This index has been shown as an interesting predictor of extubation failure in adults, but pediatric studies are lacking. ◘ Figure 12.9 provides an illustrative example of the evolution of the neuromechanical efficiency in an infant with a neuromuscular disorder. Further studies are warranted to demonstrate the impact of this monitoring on important clinical outcomes.

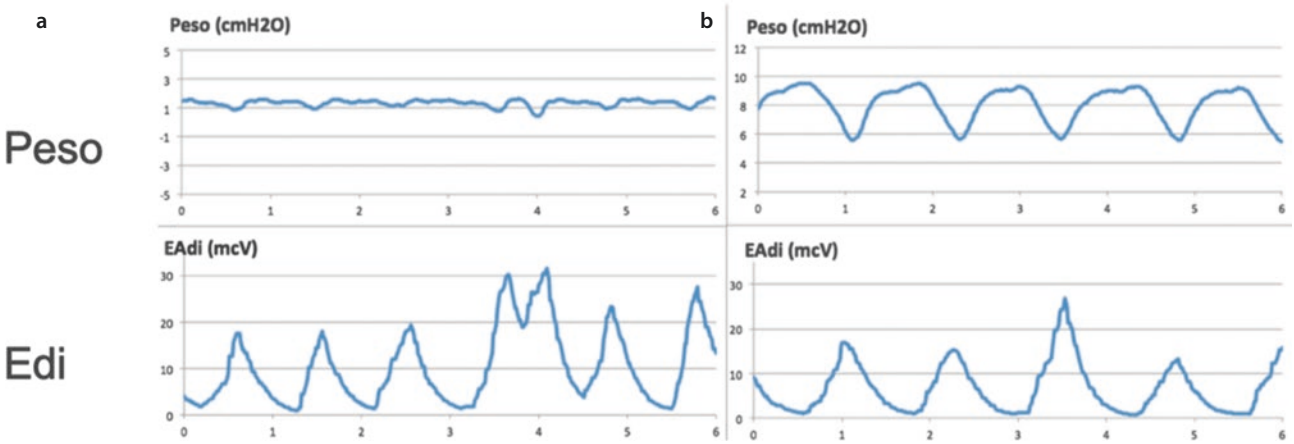

Fig. 12.9 Illustration of the neuromechanical efficiency assessed using diaphragm electrical activity (Edi) and esophageal pressure (Peso) monitoring in an infant with congenital myotonic dystrophy. Panel A illustrates this infant at 3 weeks post-term, with low esophageal pressure swings and relatively high Edi, reflecting a poor neuromechanical efficiency. Panel B shows the same infant 3 weeks later, after a respiratory weaning in NAVA ventilation. Peso swings were larger for relatively similar Edi, suggesting an improved efficiency of the diaphragm

12.4 Summary

The ability to implement and provide mechanical support to children with respiratory failure may be the single most important maneuver ever added to the ICU armamentarium. Although this technology started with the introduction of endotracheal intubation in the operating room, the more recent advances have focused on the design and function of modern mechanical ventilators which can deliver complex ventilator modes and allow precise adjustments. However, a large part of the management of pediatric mechanical ventilation is not based on strong evidence, more of which is needed. In that context, it is essential for the PICU care physician to understand the functioning and the impact of mechanical ventilation, as well as the main pathophysiological concepts leading to ventilator-induced lung injury and diaphragm dysfunction. Future studies are necessary to better understand how to best titrate the ventilation to each patient-specific condition and needs and to guide the development of future ventilators which will probably include automatic assessment and adjustment of the ventilation provided.

Review Questions

1. A 14-year-old, 50 kg male develops post-obstructive pulmonary edema following a near-hanging. He develops profound hypoxia and requires endotracheal intubation and mechanical ventilation at the referring institution. He arrives ventilated in a volume control mode. His settings are FiO_2 80%, rate 16, tidal volume 400 mL, inspiratory time 1 s, and PEEP 10 cm H_20. The PIP is measured at 34 cm H_20. He is lightly sedated but appears agitated. An arterial blood gas reveals pH 7.58, $PaCO_2$ 21 mmHg, and PaO_2 98 mmHg. The following is the most likely cause of the hypocarbia:
   A. High spontaneous rate causing excessive minute ventilation
   B. High ventilator rate causing excessive minute ventilation
   C. Large tidal volume causing excessive minute ventilation
   D. Large tidal volume causing excessive PIP
   E. Short inspiratory time allowing prolonged expiration

2. Which of the following is most correct regarding the inspiratory time in mechanical ventilation?
   A. Altering the inspiratory time in pressure-controlled ventilation can affect minute ventilation but does not affect mean airway pressure.
   B. An inspiratory pause added at end expiration does not add to the total inspiratory time.
   C. Lengthening the inspiratory time in volume-controlled ventilation can decrease the inspiratory flow and thus PIP.
   D. Longer inspiratory times help recruit alveoli with short time constants.
   E. Pressure support ventilation requires the inspiratory time be preset depending on the degree of airflow resistance or noncompliance.

3. A 9-year-old, 30 kg girl with severe influenza infection develops ARDS and progressive hypoxia. Current ventilator settings are SIMV-volume, FiO_2 100%, rate 16, tidal volume 200 mL, inspiratory time 1.4 s, and PEEP 10 cm H_2O. The PIP is measured at 40 cm H_2O, and the plateau pressure is 34 cm H_2O. Arterial blood gas reveals pH 7.28, $PaCO_2$ 51 mmHg, and PaO_2 48 mmHg. Appropriate application of PEEP is best demonstrated by:
   A. Improved oxygenation with decreased PIP
   B. Improved oxygenation with increased PIP
   C. Improved oxygenation with decreased plateau pressure
   D. Pressure volume curve demonstrating a decrease in delta volume with no change in delta pressure
   E. Pressure volume curve demonstrating an increase in delta volume with increased delta pressure

4. Pressure support ventilation is a mode that is:
   A. Patient triggered (flow or pressure), flow limited, and pressure cycled
   B. Patient triggered (flow or pressure), pressure limited, and flow cycled
   C. Patient triggered (flow or pressure), time limited, and time cycled
   D. Patient triggered (flow or pressure), volume limited, and flow cycled
   E. Time triggered, pressure limited, and flow cycled

5. A 16-year-old with chronic renal disease and long-standing hypertension presents with respiratory distress and hypertensive crisis. Admission vital signs are temperature 38.7, heart rate 108, respiratory rate 44, blood pressure 189/102, and oxygen saturation of 88% while breathing 100% FiO_2. He appears mottled with cool extremities and poor pulses. His chest radiograph shows bilateral patchy infiltrates and cardiomegaly. He rapidly progresses to respiratory failure and requires endotracheal intubation and positive pressure ventilation. Thirty minutes after intubation, his vitals are heart rate 90, ventilator rate 12, spontaneous rate 20, blood pressure 159/92, and oxygen saturation of 98% while on 60% FiO_2. He has improved color and has easily palpable pulses. He is comfortable with intermittent benzodiazepine sedation. Arterial lactate has declined to 3.5 mMol/L from 5.7 at admission. The most likely explanation for his hemodynamic improvement is:
   A. Improved oxygenation due to the application of positive pressure
   B. Positive pressure reducing afterload to the right heart
   C. Positive pressure reducing afterload to the left heart
   D. Positive pressure reducing preload to the left heart
   E. Positive pressure reducing preload to the volume overloaded right heart

6. A 2-year-old, 12 kg female develops respiratory failure due to pneumococcal pneumonia and right empyema. She undergoes video-assisted thoracoscopic surgery and has a patent draining right chest tube. She is ventilated with SIMV-volume, FiO_2 40%, rate 16, tidal volume 90 mL, inspiratory time 1.2 s, and PEEP 6 cm H_2O. The PIP is measured at 24 cm H_2O, and the plateau pressure is 20 cm H_2O. Her oxygen saturation is 98%, and she appears comfortable on a low-dose midazolam infusion and intermittent morphine. She develops acute hypoxia with oxygen saturation falling to 81%. Her lung exam is significant for equal but diminished breath sounds and no wheezing. The PIP is measured at 34 cm H_2O, and the plateau pressure is 23 cm H_2O. Her perfusion is adequate, and she is progressively agitated. The most appropriate initial intervention would be:
   A. Increase FiO_2 to 100% and administer a bronchodilator
   B. Increase FiO_2 to 100% and administer a neuromuscular blocker
   C. Increase FiO_2 to 100% and increase PEEP to 10 cm H_20
   D. Increase FiO_2 to 100% and reduce the tidal volume to 6 ml/kg
   E. Increase FiO_2 to 100% and suction the endotracheal tube

7. The optimal ventilator circuit has:
   A. Low resistance, high compliance, and nebulizer system for humidification
   B. Low resistance, high compliance, no servo-controlled heated wire system, but a rainout trap
   C. Low resistance, low compliance, and extra spacers between the Y-piece and the patient for easy patient positioning
   D. Low resistance, low compliance, and nebulizer system for humidification
   E. Low resistance, low compliance, and servo-controlled heated wire humidification system

8. Which of the following maneuvers will not increase the mean airway pressure?
   A. Adding an inspiratory pause
   B. Increasing the inspiratory time
   C. Increasing the PIP
   D. Increasing the PEEP
   E. Increasing the minute ventilation by increasing the respiratory rate at fixed I:E ratio

Answers

1. A
2. C
3. C
4. B
5. C
6. E
7. E
8. E

Suggested Readings

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Nonconventional Mechanical Ventilation

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Contents

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Learning Objectives

- Describe the patient population appropriate for consideration in the use of noninvasive mechanical ventilation.
- Understand the advantages and disadvantages of noninvasive mechanical ventilation.
- Describe the indications for use of high-frequency oscillatory ventilation (HFOV).
- Describe the "open-lung" concept.
- Understand the advantages and disadvantages of HFOV.
- Describe the mechanics of airway pressure-release ventilation (APRV).
- Describe the mechanics of high-frequency percussive ventilation (HFPV).
- Understand the population and unique needs of long-term ventilation patients.

13.1 Introduction

The evolution of care within the PICU has resulted in a population of patients surviving illnesses that previously were fatal. Mechanical ventilation is one of the major supportive therapeutic modalities used in pediatric critical care that have helped to achieve this result. Enhanced survival has led to the development of PICU survivors with residual lung disease in part secondary to the techniques used to ventilate them. The more complicated nature of mechanical pulmonary support, the desire to improve ventilator-patient synchrony, enhance patient comfort, and ease weaning from support; and the desire to minimize pulmonary trauma and to try to improve patient outcome have resulted in the introduction of many nonconventional modes of ventilation. Additionally, the desire to achieve these stated goals has also sparked an examination of less invasive forms of mechanical ventilation. Unfortunately, many of these modes of support were included into ventilators without sufficient dissemination of information regarding their use for respiratory failure. Few randomized controlled studies have been applied to these ventilation modes. This has resulted in a disparity in the variety of options available at the bedside and the knowledge to apply these modes to the pediatric population.

This chapter aims to narrow the gap between technological advancement and bedside application.

13.2 Noninvasive Ventilation

Noninvasive ventilation was one of the earliest modes of support for hypoventilatory conditions such as the polio epidemics of the mid-1900s. As the historical need for support transitioned from acute muscle pump dysfunction to one of acute pulmonary parenchymal disease, so did the transition from noninvasive to invasive support. Additionally, the development of medical devices that could deliver invasive ventilation was a prerequisite for this transition to occur. As a consequence, the use of noninvasive pulmonary support waned until the mid-1980s when a renaissance of sorts occurred in its application for treatment of acute respiratory failure. Several distinct physiologic advantages of noninvasive ventilation as well as disadvantages of invasive ventilation have fueled the reemergence of this modality.

13.3 Negative Pressure Ventilation

Negative pressure ventilation (NPV) can be defined as the application of subatmospheric pressure onto the thorax during inspiration. Historically, the initial use of noninvasive ventilation involved variations of negative pressure devices such as the iron lung. A recent FDA-approved device, the Hayek RTX oscillator is a ventilator which delivers NPV via a plastic cuirass or "turtle shell." This device has the ability to provide negative continuous pressure to the chest, similar to CPAP. It also can be set in control mode to deliver biphasic pressure, a negative pressure to augment inspiration and positive pressure to augment exhalation. Additionally, it can provide rapid alternating (oscillating) positive and negative pressures to the chest as physiotherapy to aid in secretion clearance.

NPV devices consist of two components: a ***chamber*** in which the thorax is exposed to the subatmospheric pressure and a ***pump***, which creates the pressure. All chambers used for NPV require a distance of several centimeters between the anterior chest wall and the surface of the chamber. This distance allows for anterior movement of the thorax during inspiration. The separation of the chamber and chest wall is inherent in the iron lung and cuirass ventilators.

Most pumps used for NPV are pressure-cycled and have controls for setting peak negative pressure and frequency. The ability to adjust respiratory cycle times is especially useful in younger children with their inherent need for higher breath frequency and shorter inspiratory times. Volume-cycled pumps are also available but are rarely used owing to their inability to compensate for air leaks that are commonplace with these devices.

In the PICU, the use of NPV has historically been limited to the iron lung due to its efficiency at creating a greater tidal volume per amount of negative pressure generated. The amount of tidal volume generated is related to the surface area of the thorax and abdomen over which the negative pressure is applied; therefore, the iron lung is the most efficient and the cuirass the least. Previously, the use of a cuirass was limited to the support of children with neuromuscular weakness and minimal parenchymal lung disease. Acute respiratory failure, on the other hand, was treated with the iron lung-type chamber if NPV is to be employed. However, the Hayek device has shown promise in studies for use with acute respiratory failure. In this form of ventilation, active exhalation leads to an enhanced minute ventilation and thus the ability to adequately ventilate children with parenchymal disease.

Three modes of NPV are available to accomplish the desired ventilatory goals. The most common of these modes is ***cyclical NPV*** in which the pump creates a set negative pressure to assist with thoracic expansion during inhalation. Cessation of the negative pressure and a return to atmospheric pressure upon the thorax allow for passive exhalation due to the elastic recoil of the anterior chest wall and lungs. ***Negativelpositive pressure ventilation*** uses a combination of negative inspiratory pressure and positive expiratory pressure. While infrequently used, this mode is thought to eliminate the increased functional residual capacity that exists with cuirass-type chambers. The third mode of NPV is ***continuous negative pressure*** in which a constant subatmospheric pressure exists throughout the respiratory cycle. The *negative end-expiratory pressure* (NEEP), which is present, allows for maintenance of end-expiratory volumes analogous to the positive end-expiratory pressures (PEEP) used in positive pressure ventilation. However, the negative hemodynamic consequences associated with PEEP, such as reduced venous return and depressed cardiac output, are avoided with the use of NEEP. Enhanced afterload applied

Continuous negative pressure ventilation should be cautiously applied and supported by the use of fluids and/or vasoactive infusions in children with decreased cardiac function.

upon the heart with NPV through diminished transthoracic pressures has a negligible but present effect on cardiac output. The afterload effect may be exacerbated in children with markedly depressed left ventricular function, and therefore, continuous negative pressure ventilation should be cautiously applied and assisted by the use of fluids and/or pressors in this subset of patients. Spontaneous respirations can occur throughout the NEEP period with the addition, if so desired, of cyclic increased negative pressure "breaths" imposed at a periodic predetermined rate. In children, who tend to have a greater propensity toward atelectasis related to smaller respiratory bronchioles and greater thoracic elastic recoil, the use of continuous negative pressure ventilation has become increasingly popular.

Physiologic consequences of NPV in addition to the cardiac effects noted earlier include enhancement of renal function most likely related to the augmented cardiac output. Studies have revealed that NPV results in increased free water clearance and urine volume without changes noted in urinary excretion of sodium, potassium, serum renin activity, serum aldosterone, atrial natriuretic peptide, and vasopressin levels. Less desirable side effects include the loss of coordinated upper airway reflexes frequently resulting in upper airway obstruction/apnea during sleep. Additionally, lower esophageal sphincter dysfunction has been associated with NPV resulting in increased gastroesophageal reflux disease.

Advantages of NPV include the lack of need for an artificial airway and the skilled personnel required to insert the airway. Furthermore, the complications associated with the insertion and maintenance of these airways is also avoided. Disadvantages of NPV include (1) limited access to the patient for assessment and therapeutic interventions, (2) lack of familiarity of caregivers with the use of this modality, (3) the need for skilled personnel to maintain the airway or insert an artificial airway emergently if needed due to patient deterioration, and (4) the lack of a direct conduit for assistance in removing secretions.

Historically, NPV has been used in the neonatal population to treat respiratory distress syndrome. Its use has fallen out of favor in deference to the use of positive pressure ventilation. Recently, a single-center 3-year experience using the Hayek device in pediatric acute respiratory failure was published. In this retrospective review, the authors concluded that in their population with a mean age of 15.5 months, 70% of the patients treated with NPV required no additional escalation of care. The most common diagnosis in this group was bronchiolitis. The authors noted that NPV failed primarily in patients with upper airway obstruction and also resulted in more frequent use of continuous sedation and delay in the initialization of enteral nutrition. Interestingly, they also reported a 28% decrease in the annual percentage of PICU intubations after NPV introduction when compared to the previous 3-year period.

Negative pressure ventilation (NPV) may be superior to positive pressure ventilation in children with single ventricle cardiac physiology who have undergone the Fontan procedure or have severe right ventricular restrictive physiology such as in the tetralogy of Fallot (TOF). NPV may improve pulmonary blood flow and cardiac output secondary to enhanced venous return and reduced pulmonary vascular resistance when compared to positive pressure ventilation.

Additionally, NPV has been used in children with single ventricle physiology who have undergone the Fontan procedure or have severe right ventricular restrictive physiology such as in the tetralogy of Fallot (TOF). The deleterious effects on venous return and the diminished diastolic pulmonary arterial flow associated with intermittent positive pressure ventilation (IPV) are poorly tolerated in these children. The low cardiac output state and widened arteriovenous oxygen content difference associated with these physiologic changes is reversed with the use of NPV. An early study in the 1990s demonstrated increases in pulmonary blood flow of between 40% and 80% in patients with TOF and between 42% and 52% in Fontan patients when switching from IPPV to NPV in the postoperative period. These values reversed to their previous levels when IPPV was reintroduced. In addition to the enhancement of venous return associated with NPV, another possible mechanism for this improvement includes the

reduction of elevated pulmonary vascular resistance which occurs with positive pressure inflation of the lungs beyond functional residual capacity.

In summary, NPV for acute respiratory failure and postoperative assistance with Fontan or restrictive right ventricular physiology is a viable and potentially very helpful modality for use in children. The ability to avoid ventilator-induced lung disease and endotracheal intubation and improve cardiac output warrants a more extensive reevaluation of its use in children with acute respiratory failure.

13.4 Noninvasive Positive Pressure Ventilation

Noninvasive positive pressure ventilation (NPPV) refers to the cyclical application of positive pressure ventilation without the need for an artificial invasive airway. By virtue of its effectiveness and convenience, NPPV delivered by an interface via the nose or mouth has become the preferred method of noninvasive ventilation. Traditional use for chronic ventilation needs in children with chest wall deformities, neuromuscular weakness, and central hypoventilation has recently been expanded to its use for acute hypoxic respiratory failure (HRF) and postoperative patients and to facilitate extubation in difficult-to-wean patients.

The reduction in the complications associated with invasive ventilation such as direct airway trauma, the preservation of the upper airway defense mechanisms, and the maintenance of upper airway function and comfort are some of the major reasons for the use of NPPV.

There are many compelling reasons for using noninvasive ventilation. The reduction of the complications associated with invasive ventilation such as direct airway trauma, preservation of the upper airway defense mechanisms, as well as maintenance of upper airway function and comfort are major considerations for the preferential use of NPPV. Dental, laryngeal, and tracheal injuries occur frequently. Nosocomial pneumonias facilitated by the provision of direct access to the lower airways by the endotracheal tube are well documented. The inability to eat and communicate because of the endotracheal tube contributes to the patient's anxiety and discomfort and frequently leads to the need for increased sedation and analgesia to improve ventilator-patient synchrony. By avoiding these complications, NPPV may reduce morbidity, assist with the weaning process, decrease ICU and hospital length of stay, as well as reduce overall costs and enhance patient comfort.

The mechanism by which NPPV assists ventilation is the same as for invasive PPV; supra-atmospheric pressure is applied intermittently via the airways, increasing transpulmonary pressure and inflating the lungs. Exhalation is achieved by passive lung recoil. Additionally, positive end-expiratory pressure (PEEP) and inspiratory pressure support can assist ventilation by lowering transdiaphragmatic pressure, respiratory muscle pressure-time index, and the diaphragmatic electromyographic activity. The ventilation achieved from a preset inspiratory pressure (IPAP) varies based on the mechanical characteristics of the respiratory system. These characteristics include the total thoracic compliance and resistance as well as auto-PEEP, respiratory rate, and mask leakage. An additional important characteristic of NPPV is its ability to assist spontaneous respirations. This function is initiated by either a flow or pressure trigger. In the weak or sedated child, inspiratory effort may be insufficient to activate this function and may need to be overcome by imposing a higher mandatory rate to essentially impose a controlled mode of ventilation. The expiratory trigger can either be a function of time or a reduction in inspiratory flow. In the case of expiratory flow trigger, care must be observed in children with large air leaks as a result of ill-fitting masks. In such situations, the lack of

inspiratory flow reduction can result in prolongation of inspiration by the machine beyond the child's inspiratory effort and therefore impede exhalation. Frequently, NPPV results in reductions in respiratory rate and accessory muscle use and increases in tidal volume and minute ventilation. Furthermore, enhanced oxygenation as a result of improved ventilation-perfusion matching, as well as enhanced left ventricular function, due to the afterload-reducing effects of increased intrathoracic pressure, may break the vicious cycle of worsening respiratory muscle function and gas exchange in children with acute HRF.

NPPV may result in enhanced oxygenation as a result of improved ventilation-perfusion matching as well as enhanced left ventricular function.

The lack of a direct conduit to the lower airway will inhibit direct removal of secretions. Alternative secretion management tools such as insufflation-exsufflation and high-frequency chest wall oscillation are important to assist with secretion removal and prevention of atelectasis. NPPV requires cooperation on the part of the patient to maximize its effects when treating HRF. Deep sedation and paralysis will result in less than optimal oxygenation and ventilation and therefore is difficult to use in the uncooperative or unconscious child.

Complications associated with NPPV include aspiration, gastric distension and perforation, nasal bridge irritation and ulcerations, pneumomediastinum and pneumothorax, exacerbations of gastroesophageal reflux disease, enhanced anxiety, and irritation of the eyes.

Complications associated with NPPV include aspiration, gastric distension and perforation, nasal bridge irritation and ulcerations, pneumomediastinum, and pneumothorax. Additionally, exacerbation of gastroesophageal reflux disease, enhanced anxiety, and eye irritations are not infrequently reported adverse effects.

Experience with NPPV in children is limited but growing in the treatment of acute respiratory failure (ARF). Extensive use of NPPV exists in the neonatal and adult literature for the treatment of ARF secondary to neonatal RDS, COPD, pulmonary edema, pneumonia, and ARDS.

Early reports describe a small number of patients in which NPPV was used to assist with extubation and avoid reintubation. A retrospective report published in 1995 described the successful use of NPPV in children with various causes of HRF for both avoidance of intubation or reintubation. In this report, 9 of 10 children were able to avoid intubation, and 16 of 18 children were able to remain extubated with the assistance of NPPV. Shortly thereafter, a prospective study of 34 patients with 35 episodes of acute respiratory failure and hemodynamic stability reported that avoidance of intubation was accomplished in 91% of HRF episodes.

Use of NPPV in status asthmaticus has been reported in a number of studies. A review of status asthmaticus with hypoxemia reported that 19 of 26 patients were able to avoid intubation when using a nasal interface. Another report described 5 children with status asthmaticus who used NPPV for a mean duration of 33 hours and resulted in significant improvement in respiratory rate and modified Pulmonary Index Score. A subsequent study prospectively assessed the use of NPPV in 20 children with lower airway obstruction. Results of this study included a reduction in Clinical Asthma Score as a result of reduction in respiratory rate, accessory muscle use, and dyspnea when compared to standard therapy. Only one patient in this study required mechanical ventilation; however, the authors admitted that the incidence of intubation for asthma at baseline within their institution was quite low and therefore was not a useful outcome variable.

NPPV may therefore be beneficial in a variety of acute disorders resulting in HRF. In addition to avoiding the use of endotracheal intubation and its associated complications, other potential benefits such as reduction in length of stay, diminished use of sedatives, improved patient comfort, and reduction of PICU costs will need to be evaluated in a large prospectively randomized study.

13.5 High-Frequency Oscillatory Ventilation

Since the early 1990s, the importance of opening the lung and keeping it open has been described and accepted. Emphasis has been placed on the benefit of small-pressure amplitudes to prevent lung damage due to shearing forces and minimize surfactant loss. Related concepts included the benefits of intrinsic PEEP due to shortened expiratory times which contributes to the maintenance of airway recruitment of noncompliant lung units while allowing ventilation to occur at markedly lower amplitudes than what is used in conventional ventilation. High-frequency oscillatory ventilation (HFOV) applies these concepts to their fullest extent. HFOV preserves end-expiratory lung volumes and minimizes cyclic stretch while avoiding overdistension at end inspiration by using tidal volumes, which approach or are smaller than the anatomic dead space. The use of high mean airway pressures (P_{aw}) results in the recruitment and maintenance of lung units. Superimposed upon this P_{aw} are sinusoidal pressure oscillations at a frequency of 3–15 Hz.

Mechanisms of gas transport in HFOV have been elucidated through experimental animal work. CO_2 elimination is a function of the frequency and the square of the tidal volume ($VCO_2 = f \times Vt^2$). Tidal volume correlates with the amplitude of oscillation (Δ P) and is inversely related to frequency (Hz). Recruitment of alveoli is related to the P_{aw} and the inspiratory to expiratory time ratio (I:E). Direct bulk airflow can account for only proximal alveolar units and the major airways. Asymmetry of the gas flow profile during different phases of the ventilator cycle (parabolic in one phase and square in the other phase) results in a flow of gas in one direction through the center of the airway and in the other direction along the periphery. Augmented dispersion is a concept of gas dispersion first described in 1953 by Geoffrey Taylor. This theory states that gas dispersion results from the interaction along the profile of high-velocity gas flow and the radial diffusion of gases in motion. Therefore, net transport of gases occurs beyond the bulk flow front. Interregional gas mixing occurs due to asymmetry of alveolar time constants. In this concept, units with short-time constants fill and empty rapidly. At the end of exhalation, the fast units are empty and ready to fill, whereas the slow units are still emptying. Consequently, gas moves from the slow units to the fast units. During inspiration, the opposite occurs with gas moving from the fast units to the slow units. This movement has been named pendelluft movement. Pendelluft may play a larger role in lung disease with heterogeneous injury. Finally, as in conventional ventilation, molecular diffusion results from random motion of gas molecules resulting in gas transport across the alveolar membrane. Additionally, in HFOV, a diffusion gradient is generated from the mouth (high O_2) to the alveolus as O_2 is transported into the pulmonary circulation (low O_2). Likewise, a similar gradient in the opposite direction assists with CO_2 elimination (◘ Fig. 13.1).

Carbon dioxide (CO_2) elimination is a function of the frequency (f) and the square of the tidal volume (Vt): [$VCO_2 = f \times (Vt)^2$] in HFOV. The tidal volume correlates with the amplitude of the oscillation (ΔP) and is inversely related to the frequency (Hz).

Several mechanisms have now been described that contribute to gas exchange in HFOV including bulk convection, asymmetric velocity profiles, Taylor dispersion and turbulence, pendelluft, molecular diffusion, and collateral ventilation.

When initiating HFOV, optimization of PaO_2 occurs in a linear fashion as lung volume is increased up to a point when alveolar overdistension occurs. This open lung strategy may be accomplished by initially setting P_{aw} 4–5 cm H_2O above the P_{aw} used during conventional ventilation. This is done to maintain airway recruitment and to counteract the known attenuation of P_{aw} by the endotracheal tube. P_{aw} does not equate with alveolar pressure both due to this attenuation and because exhalation in HFOV is active which results in some airway collapse and the generation of a pressure gradient between proximal and distal airways. Additionally, pressure oscillations are less dampened in atelectatic lungs, thereby exposing the conducting airways to higher and poten-

When initiating HFOV, the mean airway pressure (P_{aw}) is set at 4–5 cm H_2O above the P_{aw} used during conventional ventilation. This increment is utilized to maintain airway recruitment and to counteract the attenuation of P_{aw} by the endotracheal tube.

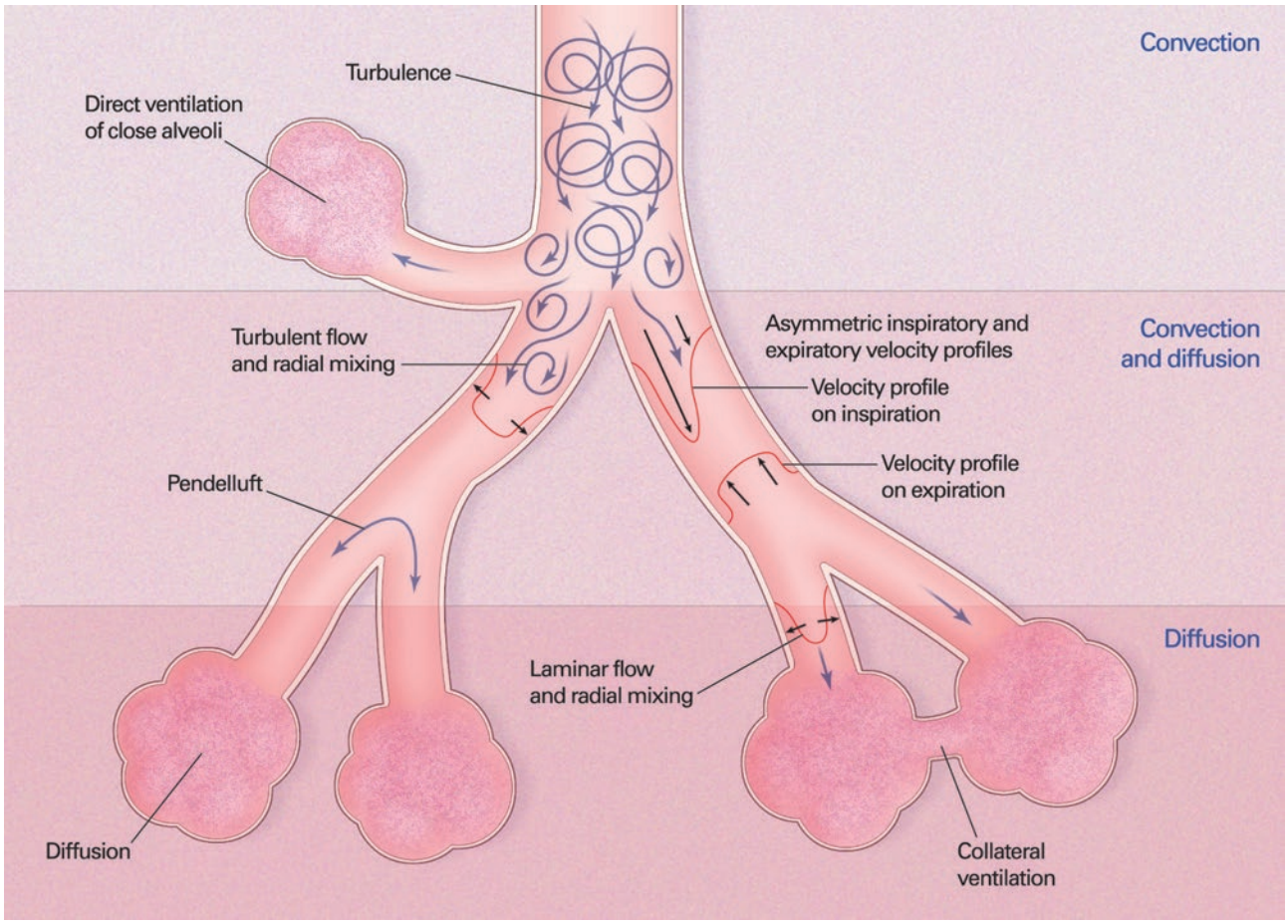

Fig. 13.1 Schematic of gas exchange during high-frequency oscillatory ventilation. (Slutsky 2002)

Hypoxemia is treated by adjusting the P_{aw} upward in small increments (1–2 cm H_2O).

Historically, the HFO frequency is set based on the age and size of the patient with higher levels (12–15 Hz) used in infants, moderate levels (8–12 Hz) in young children, and low levels (3–8 Hz) in older children and adolescents. Newer approaches take into consideration the disease characteristics of lung compliance and airway resistance.

tially injurious pressure swings. Additional elevations of Paw above the initial 4–5 cm initially applied may be required to adequately recruit otherwise unexpanded lung units. In addition to the elevation of Paw, recruitment maneuvers such as sustained dynamic inflation episodes or stepwise pressure increases over 5–6 minutes may be useful.

In practice, the initial 4–5 cm H_2O P_{aw} pressure increase over conventional ventilation should be followed with additional small increments (1–2 cm H_2O) in P_{aw} to a point when oxygenation does not improve with a fixed FiO_2. As airways are recruited, a concomitant decrease in amplitude (ΔP) may be noted as a function of improving compliance, approximating total lung compliance (TLC). Subsequently, P_{aw} may be weaned to a point when oxygenation begins to deteriorate, consistent with derecruitment. Additionally, amplitude may again increase consistent with derecruitment.

Historically, it has been recommended setting the frequency (f) based on the patient's age and observation of chest wiggle adjusted to achieve adequate vibrations to the abdominal or groin level. Higher levels (12–15 Hz) are used in infants, moderate levels (8–12 Hz) in young children, and low levels (3–8 Hz) in older children and adolescents. However, an approach to improvements in ventilation should also be determined by lung characteristics and the disease process. With decreased compliance due to atelectasis, there is a significant increase in ΔP peak-to-trough transmission in the distal airways and alveoli. Conversely, increased resistance of the lung results in decreased peak-to-trough transmission distally in the airway and alveoli. Therefore, in diseases such as ARDS, it

may be wise to use the highest possible f since it determines the rate of oscillations and directly influences Vt. Because f is inversely proportional to Vt, a higher f results in a smaller Vt. Therefore, using a higher f makes it easier to avoid dynamic hyperinflation and possible lung injury. An additional method to prevent overdistension is achieved by keeping the diaphragm between the eighth and tenth posterior ribs on an anteroposterior chest X-ray. Consequently, once optimal f is chosen, the ΔP is titrated, in 2–3 cm H_2O increments to achieve optimal CO_2 elimination. In patients with increased airways resistance, a lower f, in theory, may be beneficial to allow for adequate delivery of a larger Vt to the distal airways. As in lung diseases with poor compliance, the ΔP is titrated to achieve adequate CO_2 elimination. Additional ways to treat hypercarbia include decreasing the frequency in 0.5–1 Hz increments, or partially deflating the endotracheal tube cuff, if present.

In patients with air leak, after initial airway recruitment, P_{aw} may be lowered in small increments until a point is reached at which the air leak is eliminated. In such cases, optimization of oxygenation is likely to require FiO_2 ≥60%, and acceptance of higher levels of CO_2 will likely be necessary. Alternatively, similar results may be achieved with higher frequencies and shorter inspiratory times.

Weaning a patient from HFOV can be considered when clinical improvement allows progressive diminishment of P_{aw} while maintaining FiO_2 of ≤60%. While neonatal literature reports the successful liberation of infants directly from HFOV, this is not able to be accomplished in older children. This is due to the difficulty of allowing children to spontaneously breathe while on HFOV. While spontaneous breathing during HFOV may result in improved oxygenation and ventilation, it is only feasible for small children owing to their smaller airflow demands. The larger child's airflow demands exceed the maximal possible bias flow delivered by the oscillator, therefore leading to increased work of breathing. Because of this, older and larger children will require deep sedation and probable neuromuscular blockade in order to prevent spontaneous breathing. Therefore, transition from HFOV is usually to a form of conventional ventilation. Consideration of this transition generally may occur when P_{aw} ≤20 cm H_2O and the FiO_2 remains ≤60%. As noted earlier, due to attenuation of P_{aw} by the endotracheal tube, the P_{aw} of conventional ventilation can frequently be significantly lower than was present on HFOV prior to the transition.

Few good studies have been performed to compare HFOV with conventional ventilation in pediatric patients with HRF. Recently, two randomized adult trials (OSCILLATE and OSCAR) have been published and reported poorer mortality outcomes for HFOV compared to conventional ventilation in the treatment of HRF. Subsequently, a retrospective multicenter pediatric study, utilizing propensity score matching, compared HFOV and conventional ventilation in the treatment of HRF in children. The study noted that HFOV had significantly worse outcomes in terms of length of mechanical ventilation, ICU length of stay, and mortality. The study was criticized for many reasons including its retrospective design, its inclusion criteria, and its statistical approach in multiple editorials and letters to the editor. To date, there have been no prospective randomized trials of comparing HFOV and conventional ventilation in HRF. Thus, we are left with numerous case reports using HFOV as rescue therapy for patients with HRF who failed conventional ventilation. The reports have contributed little to the knowledge base as to its suitability as primary therapy but have expanded the experience and familiarity with its use for pediatric practitioners. Only one multicenter randomized crossover study has been reported in children with HRF and/or

During HFOV, the lungs should be inflated such that the diaphragm lies between the eighth and tenth posterior ribs on an anteroposterior chest radiograph.

Hypercarbia is treated by increasing the amplitude in 2–3 cm H_2O increments, decreasing the frequency in increments of 0.5–1 Hz, or partially deflating the endotracheal tube cuff.

air leak. In this study, 70 patients were randomized to either conventional ventilation using a limited pressure strategy or HFOV. Results of this study found no difference in survival or duration of mechanical ventilation. However, significantly fewer patients in the HFOV arm of the study required mechanical ventilation at 30 days after entry. Additional post hoc analysis revealed that those patients that crossed over to the HFOV study arm did not benefit as well as those patients placed on HFOV primarily. This reinforces the generally held belief that in order to be successful, alternative modes of ventilatory support must be invoked before irreversible lung injury has occurred. More recently, a retrospective analysis has been performed in patients with HRF who were initially managed with conventional mechanical ventilation strategies and subsequently transitioned to HFOV. Significant improved outcomes were obtained in patients transitioned to HFOV prior to 24 hours after initiation of mechanical ventilation. In patients evenly matched for Oxygen Index and risk of mortality, a 59% survival was achieved in patients transitioned to HFOV in the early group and 13% in those who were placed on HFOV beyond 24 hours.

In conclusion, HFOV remains an option in the treatment of HRF. Experience with HFOV has proven its safety in the PICU although its efficacy remains in question. Larger studies as well as earlier implementation during HRF may elucidate further benefits. Additionally, improved methods at determining optimal alveolar expansion may better enable optimization of HFOV settings perhaps leading to better outcomes.

13.6 High-Frequency Percussive Ventilation

High-frequency percussive ventilation (HFPV) is a form of high-frequency ventilation, which delivers subphysiologic volumes at rapid rates via the volume-diffusive respirator (VDR).

The subtidal volume impulses are superimposed on a conventional pressure-controlled, time-cycled ventilator (CV) usually set at a rate of 10–15 breaths per minute.

Numerous case reports have documented the successful use of HFPV to improve oxygenation and ventilation in the neonatal and pediatric population for acute respiratory failure, ARDS, and inhalational injury.

High-frequency percussive ventilation (HFPV) is a form of HFV, which delivers subphysiologic volumes at rapid rates via the volume-diffusive respirator (VDR). The VDR is a pneumatically powered time-cycled, pressure-limited ventilator with inspiratory and expiratory oscillation. The VDR has a phasitron (Venturi mechanism) positioned in the proximal airway, which delivers timed impulses of subtidal volumes of respiratory gases at a frequency of 200–900 beats/min. The subtidal volume impulses are superimposed on a conventional pressure-controlled cycle ventilator (CV) usually set at a rate of 10–15 breaths/min. Physiologically, the stepwise inflation of the lungs diffuses O_2 distally into the airway while also mechanically mixing returning alveolar CO_2 entering the peripheral airways. On inspiration, a diaphragm connected to the phasitron fills with gas and pushes it forward, blocking the expiratory ports, and the jet delivers short percussive pulsations. Due to the high-pressure gradient at the start of inspiration between the mouth and alveolus, a large amount of air is entrained. As the gradient drops during inspiration, air entrainment and total flow decrease, but the jet pulsations continue. During this period, oscillatory equilibrium occurs at which time no further alveolar inflation occurs, and percussive mixing of intrapulmonary gases takes place. When the time limit is reached, the CV cycles off; however, the phasitron continues to fire. PEEP is maintained by a set flow as the expiratory limb opens and expiration takes place passively until reaching a preset baseline pressure. The endotracheal tube cuff, if present, is partially deflated to assist with mobilization of secretions, which occurs from the continuous application of percussive forces. Additional benefits of cuff deflation include enhanced elimination of CO_2 and avoiding the generation of dangerous intra-alveolar pressures.

Numerous case reports have documented successful use of HFPV to improve oxygenation and ventilation in the neonatal and pediatric population for both acute respiratory failure/ARDS and inhalational injury. Additionally, there have been two prospective randomized controlled studies in the use of HFPV for pediatric burn patients. One study randomized 43 patients to CV or HFPV following inhalational injury. HFPV was found to provide adequate ventilation at significantly reduced PIPs (30 vs. 43 cm H_2O) as well as a trend toward lower rates of pneumonia and mortality rates. A subsequent prospective study randomized 64 children to HFPV and low-volume (6–8 ml/kg) pressure-controlled ventilation. This study demonstrated enhanced oxygenation and ventilation with lower PIPs (30 vs. 39 cm H_2O) but again revealed no difference in pneumonia, ARDS, sepsis, or mortality.

Two prospective, randomized, controlled studies of the use of HFPV for pediatric burn patients found HFPV to provide adequate oxygenation and ventilation at significantly reduced peak inspiratory pressures than conventional ventilation.

One small (31 patients) single-center, observational study of pediatric ARF described the effectiveness of HFPV in patients who failed conventional ventilation. The authors concluded that significant improvements in oxygenation index, oxygen saturation index, PaO_2/FiO_2, and oxygen saturations were present as early as 12 hours and persisted through 48 hours after transition. Additionally, significant reductions in $PaCO_2$ were present within 6 hours and persisted through 48 hours after transition. Furthermore, these improvements in gas exchange were achieved with reduced peak inflating pressures throughout the study period. Most importantly, the authors reported that 84% of the transitioned patients survived to hospital discharge.

Although no studies have been reported in children, several adult reports have indicated possible benefits in HFPV in patients with head injury associated with increased intracranial pressure (ICP) in the presence of ARDS. These studies have demonstrated significant improvement in oxygenation, ventilation, and lowering of ICP when compared to CV.

HFPV may provide an alternative to CV in the treatment of ARF and inhalational injuries. HFPV may improve oxygenation and ventilation as well as improve mobilization of airway secretions and debris while lowering inspiratory pressures and potentially reducing risk of barotraumas.

13.7 Airway Pressure-Release Ventilation

Airway pressure-release ventilation (APRV) is a time-triggered, pressure-limited, and time-cycled mode of ventilation specifically intended for patients with a sustained spontaneous respiratory effort. Although in theory APRV can also accomplish complete ventilation in patients without spontaneous respiratory effort, it is rarely applied this way in pediatric patients. APRV is reported to reduce the discomfort associated with pressure-controlled ventilation and provides the advantages of pressure limitation.

Airway pressure-release ventilation (APRV) is a time-triggered, pressure-limited, and time-cycled mode of ventilation specifically intended for patients with a sustained spontaneous respiratory effort.

APRV consists of a high-flow continuous positive airway pressure (CPAP) around which patients can spontaneously breath. Additionally, there are regular, intermittent "breaths" accomplished by opening of the expiratory valve resulting in an abrupt, brief lowering of circuit pressure that allows outflow of gas from the lungs (release volume). This results in alveolar ventilation and removal of CO_2. APRV can be thought of as two levels of CPAP ventilation with the majority of the time spent at the higher level of CPAP. Unlike CPAP, APRV can improve both oxygenation and ventilation through this combination of elevated P_{aw}, timed releases, and spontaneous efforts.

In addition to FiO_2, the settings applied in APRV revolve around establishing the high- and low-pressure levels, as well as time intervals for which each of these pressure levels exist. These settings are designated as pressure high (P_{high}),

pressure low (P_{low}), time high (T_{high}), and time low (T_{low}). The conventional application of these settings includes a P_{high} equivalent to the plateau pressure during conventional ventilation, in the 20–35 cm H_20 range. A T_{high} in the 4–10 seconds range with P_{low} established between 0 and 4 cm H_2O, and T_{low} between 0.2 and 0.8 seconds. With such long inspiratory times and diminished expiratory times, APRV, without spontaneous respiratory effort, could be described as an extreme version of inverse ratio ventilation. Increases in oxygenation are established through manipulation of mean P_{aw} as described by the equation:

$$\frac{\left(P_{high} \times T_{high}\right) + \left(P_{low} \times T_{low}\right)}{\left(T_{high} + T_{low}\right)}$$

Tidal (release) volume is established by the amount of difference in the two pressures and can vary based on the thoracic compliance, resistance, and the T_{low}. As alveoli recruitment occurs, the "release" volumes progressively increase.

Tidal (release) volume is established by the amount of difference in the two pressures and can vary based on the thoracic compliance and resistance, as well as the T_{low}. As alveoli recruitment occurs, the "release" volumes progressively increase.

The use of recruitment maneuvers has been shown to improve gas exchange and compliance, although these effects appear to be nonsustained, requiring repeated application. Alternatively, APRV may be viewed as a nearly continuous recruitment maneuver, where the P_{high} creates a stabilized "open lung" while at the same time facilitating spontaneous breathing.

APRV additionally augments oxygenation and ventilation in low-compliance pulmonary diseases by reducing shunting caused by diminished FRC from collapsed alveoli. The recruitment of alveoli through the use of prolonged plateau pressures allows collateral ventilation through the pores of Kohn, the canals of Lambert, and the channels of Martin to assist in the expansion of lung units with long time constants or decreased compliance. The efficiency of collateral ventilation is enhanced with decreased ventilator frequency, thus establishing APRV as an optimal choice to enhance alveolar recruitment through these pathways.

Ventilation may be enhanced by increasing the frequency of depressurization cycles, reducing impedance to expiratory flow by reducing P_{low}, lengthening the duration of depressurization (T_{low}), or treating bronchospasm.

The allowance of unrestricted, spontaneous breathing throughout the respiratory cycle improves patient comfort, eliminates patient-ventilator dyssynchrony, and theoretically diminishes the need for sedation and paralysis. Thorough engagement of the diaphragm by spontaneous breathing has been shown to distribute ventilation in a different pattern than mechanical or assisted breaths. Whereas mechanical breaths preferentially ventilate poorly perfused, well-aerated, nondependent lung units, spontaneous breaths tend to ventilate well-perfused, underaerated, dependent alveoli. This results in enhanced ventilation-perfusion matching and diminished dead space ventilation. An additional benefit of spontaneous ventilation is achieved by decreasing intrathoracic pressures, thus enhancing venous return and cardiac index.

Oxygenation is improved by increasing the level of P_{high} (recruiting alveoli with higher opening pressures), increasing the T_{high} (enhancing collateral circulation and recruitment of lung units having high resistance), increasing the P_{low} (preventing derecruitment), or shortening the T_{low} of the release breath (increasing intrinsic PEEP).

The clinician determines the frequency, magnitude, and length of the depressurization cycles in response to the patient's ventilation needs. Increasing the frequency of depressurization cycles enhances ventilation. Reducing impedance to expiratory flow by reducing P_{low}, lengthening the duration of depressurization (T_{low}), or treating bronchospasm also increases release volumes and improves ventilation. Conversely, systemic oxygenation improves by increases in P_{aw}, increasing the level of P_{high} (recruiting alveoli with higher opening pressures), increasing the T_{high} (enhancing collateral circulation and recruiting lung units having high resistance), increasing the P_{low} (prevent derecruitment), or shortening the T_{low} of the release breath (increase intrinsic PEEP). Usual practice for setting T_{low} involves adjusting the time such that expiratory flow during the release phase reaches 50–75% of its peak value (i.e., expiratory flow and exhalation are not complete).

Data on clinical outcomes in pediatric patients using APRV are limited to case series and a single small crossover design study. More recently, a retrospective, single-center moderately large (104 patient) study reported on the use of either HFOV or APRV in pediatric patients failing conventional ventilation. This study reported a mortality rate of 39% in this patient population, consistent with the rate found in NCV use for respiratory failure in other studies. Interestingly, this study noted that survival was associated with a nearly doubling of oxygenation after 24 hours compared to oxygenation improvements in non-survivors.

Therefore, routine use of APRV in ALI cannot be advocated on the basis of clinical information available today. However, the potential benefits of reduced peak inspiratory pressures, enhanced oxygenation and ventilation, reduced neuromuscular blockade and sedation, as well as improved hemodynamics warrant consideration for its use in patients with deteriorating clinical conditions with conventional mechanical ventilation. As discussed earlier in this chapter, larger studies as well as earlier implementation during HRF may elucidate further benefits. APRV is an alternative consideration in the spontaneously breathing patient who requires mechanical ventilation support yet experiences significant discomfort or potentially dangerous pressures with conventional ventilation. APRV may be combined with pressure support, tracheal gas insufflation, or prone positioning to further support the patient's respiratory efforts and has been used in the setting of ARDS in both adult and pediatric patients.

APRV may be considered an alternative for the spontaneously breathing patient who requires mechanical ventilation support requiring potentially toxic pressures or experiencing significant discomfort with conventional ventilation.

13.8 Long-Term Mechanical Ventilation

Patients requiring prolonged mechanical ventilation are rapidly increasing in number. Improved ICU care has resulted in many patients surviving acute respiratory failure to require prolonged mechanical ventilation during convalescence. Also, mechanical ventilation is increasingly used as a therapeutic option for patients with symptomatic chronic hypoventilation, with an increased effort to predict nocturnal hypoventilation to initiate ventilation earlier. Unfortunately, there are no comprehensive databases or national registry of home ventilator patients—therefore, the precise number of home ventilator patients is unknown.

A 2011 review of the Kids Inpatient Database produced by the Agency for Healthcare Research and Quality for the years 2000–2006 found that there were an estimated 7812 discharges associated with long-term mechanical ventilation (LTMV). Compared to discharges for children with complex chronic conditions (CCCs), LTMV had significantly higher mortality, longer lengths of stay, higher mean charges, more emergency department admissions, and more discharges to long-term care. From 2000 to 2006, there was a 55% increase in the number of LTMV discharges and a concurrent 70% increase in hospital charges. The majority of LTMV discharges occurred in children under 4 years of age with approximately 50% of the charges attributed to children <1 year old. To my knowledge, no comprehensive review has been compiled regarding pediatric LTMV in the ensuing decade.

A nationwide review of pediatric inpatient discharges showed that compared with discharges for other children with complex chronic conditions, long-term ventilated patients had significantly higher mortality, longer lengths of stay, higher mean charges, more emergency department admissions, and more discharges to long-term care.

Mechanical ventilation in the home is not a new idea. Patients with poliomyelitis benefited from home mechanical ventilation by iron lung during the years before the 1950s. With the development of positive pressure ventilators, home use of these devices with tracheostomies emerged as a viable technology. In 1977, the LP3 portable volume ventilator was approved by the FDA for use outside the hospital. The initial target population for home mechanical ventilation was ventilator-dependent pediatric patients. This effort was led by Dr. Allen Goldberg, who learned of this approach in France and returned to Children's Hospital of Pennsylvania to begin the first home ventilator program there.

The population of children receiving long-term mechanical ventilation outside of the acute care setting has grown dramatically over the last two decades but with no comprehensive review of their numbers, characteristics, and outcomes.

An important reimbursement milestone occurred in 1981 with Katie Beckett, an infant with viral encephalitis that left her ventilator-dependent in a pediatric ICU in Iowa. Officials from Medicaid, the government health insurance plan for the needy, initially claimed that it could only pay for her care in the pediatric ICU. At the behest of her family (and others), the Medicaid waiver program (sometimes referred to as the "Katie Beckett waiver") was passed. This program allowed parents like the Becketts, who made too much money to qualify for Medicaid, to be covered for their child with extreme medical costs, even though their child lived at home instead of in an institution. Technology, expertise, and funding were now available to support ventilator-dependent patients outside of the hospital.

Ideally, the preferred location for long-term mechanical ventilation is in the home because costs are reduced, quality of life is enhanced, and integration into the community is maximized. For the pediatric ventilator patient, the advantages of home ventilation also include being reunited with parents and family, which greatly enhances normal development and relationships. Home mechanical ventilation also reduces exposure to hospital-borne infections and frees hospital ICU beds for other acutely ill patients.

The indications for mechanical ventilatory support in the home are increasing as technology and infrastructure support improve. However, the levels of support and the goals of support can differ substantially, depending upon a number of factors. For example, some conditions may require support only at night and/or intermittently during waking hours. Other conditions, however, require high levels of support 24 h/d. Disease trajectory can also affect goals and planning. For example, a slowly improving process (e.g., premature infants recovering from chronic lung disease of infancy) may warrant plans for weaning the support. On the other hand, progressive respiratory failure (e.g., adolescents with Duchenne muscular dystrophy) will need the incorporation of plans for future palliative care.

In light of this growing population, the pediatric intensivist's exposure to this patient population has also grown exponentially. While encountering these patients with acute illnesses is common, the care of these patients is not dissimilar to other PICU patients with CCCs. Depending on the particular PICU in which the practitioner practices, one may also require involvement in the decision-making, home caregiver training, and the delineation of home medical equipment in the patient readying for their initial discharge to home. This preparation can entail a lengthy process lasting for weeks to months. When caring for such a patient, one of the most challenging aspects the pediatric intensivist will encounter is changing their own mindset. As opposed to the acutely ill PICU patient, LTMV patients preparing for discharge by definition are clinically stable and do not require frequent laboratory testing or radiologic examination. Likewise, every perturbation in oxygen saturation, O_2 requirement, or episode of agitation does not necessarily require specific and aggressive intervention. Additionally, the comprehensive care required by the children will require the intensivist to address areas of care not frequently encountered in caring for typical PICU patients. Areas to address include long-term weaning goals, preparation for emergency situations at home, determination of environment of care (home, long-term care facility, foster care), activities of daily living, mobility, communication, as well as psychosocial concerns for both the patient and their family. As the training and exposure of most pediatric intensivists is somewhat limited in this patient population, it would behoove the intensivist to avail themselves of the expertise of pediatric pulmonologists, rehabilitation professionals (occupational, physical, and speech therapists), and social workers to assist them in developing the comprehensive outpatient care plan that these complex patients require.

13.9 Conclusion

Nonconventional modes of mechanical ventilation have no prospective large randomized clinical studies establishing their efficacy in the use for pediatric patients with acute respiratory failure. The use of these modes of ventilation is best reserved for clinical failures of conventional ventilation and in those patients who may benefit from avoidance of the negative consequences of such ventilation. Outcome studies and multicenter randomized trials of various forms of nonconventional ventilation would be helpful in establishing proper boundaries for use of these modes in pediatric patients.

Review Questions

1. Negative pressure ventilation is MOST likely to benefit which of the following causes of respiratory failure?
   A. Acute pulmonary edema
   B. Bronchiolitis
   C. Increased intracranial pressure
   D. Left-sided myocardial dysfunction
   E. Neuromuscular disease with minimal parenchymal lung disease

2. Noninvasive positive pressure ventilation is most likely to be beneficial in which of the following patients?
   A. Cooperative 7-year-old with status asthmaticus
   B. Fourteen-year-old with traumatic brain injury and facial trauma
   C. Two-year-old with pneumonitis following lye ingestion
   D. Anxious 8-month-old with abdominal distention and gastroesophageal reflux-induced bradydysrhythmias
   E. Obtunded 14-year-old with suspected encephalitis.

3. A 5-year-old with acute hypoxemic respiratory failure is being supported with high-frequency oscillatory ventilation requiring 100% oxygen. His most recent arterial blood gas reveals a pH of 7.38, a $PaCO_2$ of 52 mm Hg, a PaO_2 of 47 mm Hg, and an oxygen saturation of 81%. Chest radiograph reveals no evidence of a pneumothorax and lung expansion to the eighth rib posteriorly. The most appropriate ventilator adjustment would be to:
   A. Adjust the I:E ratio
   B. Increase the amplitude by 2 cm H_2O
   C. Increase the frequency by 2 Hz
   D. Increase the mean airway pressure by 2 cm H_2O
   E. Partially deflate the endotracheal tube cuff

4. In comparison to conventional ventilation, the use of high-frequency percussive ventilation in pediatric patients with inhalational injury has been found to be associated with:
   A. Decreased lengths of mechanical ventilation
   B. Decreased mortality
   C. Decreased peak inspiratory pressures
   D. Increased incidence of pneumonia
   E. Lower PaO_2/FiO_2 ratios

5. A 12-year-old male with acute respiratory distress syndrome is being supported with airway pressure-release ventilation requiring 100% oxygen. His most recent arterial blood gas reveals a pH of 7.37, a $PaCO_2$ of 53 mm Hg, a PaO_2 of 49 mm Hg, and an oxygen saturation of 83%. Which of the following interventions would be MOST likely to improve his oxygenation?
   A. Administering a dose of neuromuscular blockade
   B. Decreasing the P_{low}
   C. Decreasing the T_{high}
   D. Increasing the P_{high}
   E. Increasing the T_{low}

6. Care of children receiving long-term mechanical ventilation, when compared to other children with complex chronic conditions, has been demonstrated to involve which of the following?
   A. Shorter length of stay since then they can be discharged while on a ventilator
   B. Increased mortality
   C. Lower average costs
   D. Fewer emergency department visits
   E. Greater likelihood of discharge to home care

7. Which of the following represents the most beneficial effect of utilizing airway pressure-release ventilation (APRV) for the treatment of severe acute respiratory distress syndrome requiring mechanical ventilatory support with potentially toxic pressures?
   A. APRV allows for the preservation of spontaneous ventilation.
   B. APRV enhances the removal of CO_2 via collateral ventilation.
   C. APRV is associated with a lower incidence of nosocomial infections.
   D. APRV maintains favorable hemodynamics.
   E. APRV maintains the recruitment of collapsed alveoli.

Answers

1. E
2. A
3. D
4. C
5. D
6. B
7. A

Suggested Readings

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Cardiovascular

Contents

Hemodynamics

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Learning Objectives

Cardiac Physiology and Function

- State the importance of cardiac histology and anatomy as it relates to the normal cardiac cycle.
- Describe the relationship between chemical and cellular events in the myocardium and the normal cardiac cycle.
- Describe how pathologic states can alter the normal chemical and cellular events in the heart. Understand how these chemical and cellular changes affect the overall function of the heart and cardiac output.
- Summarize the components of cardiac output and the physiologic response to low cardiac output states at different ages.
- Summarize the cardiovascular response to alterations in intravascular pressure and volume.
- Discuss afterload physiology and the effect of changes in afterload on cardiac function.

Cardiopulmonary Interactions

- Describe the relationship between the function of the pulmonary and cardiovascular systems under normal conditions.
- Describe how pathologic cardiovascular and pulmonary states alter cardiopulmonary interactions.
- Discuss how positive and negative pressure ventilation affect cardiovascular physiology in the presence of normal and altered cardiovascular function.
- Explain the relationship between pulmonary and cardiovascular function in patients with single ventricle physiology/Fontan.

14.1 Introduction

In critical care, nothing is for free; the art of critical care is using a strong knowledge of physiology to optimize interventions to balance their effects between the heart and lungs.

The cardiovascular system is responsible for providing adequate blood flow to meet the metabolic demands of the body and its organs. The principles governing blood flow and pressure in the vascular system are referred to as hemodynamics. The most significant function of the cardiovascular system is the delivery of oxygen to meet the demand for cellular oxygen consumption. Although increases in oxygen delivery can occur over time through an increase in hemoglobin concentration, during an acute illness, the primary physiologic response to an increase in oxygen demand is an increase in cardiac output. If cardiac output is not sufficient to meet the metabolic needs of the body as a whole, a redistribution of regional blood flow and constriction of venous capacitance vessels must occur to maintain adequate oxygen delivery to vital organs. If the redistribution of blood flow is insufficient to meet the metabolic demands of a specific organ, organ dysfunction will begin to develop. The cardiovascular system of an otherwise healthy child with acute illness will typically perform this function well, but in the critically ill child, the physiologic response to increasing oxygen demand may be inadequate and unable to meet the metabolic needs of the body. Caring for the child with critical illness often requires interventions by the intensivist to balance oxygen and nutrient delivery with oxygen consumption and waste removal. In some cases, therapeutic interventions to support one system, such as positive pressure mechanical ventilation to support breathing, will have both beneficial and undesirable effects on the cardiovascular system. When caring for the critically ill child, it is essential to have a fundamental understanding of normal cardiac physiology, cardiopulmonary interactions, and how critical illness and therapeutic interventions can alter cardiovascular function. This chapter reviews the physiology and function of the heart and how critical illness alters cardiovascular

physiology. In addition, the unique interactions that occur between the heart and lungs will be discussed in both the healthy and ill child, including the unique cardiopulmonary interactions in a child with single ventricle anatomy.

14.2 Cardiac Physiology and Function

14.2.1 Cardiac Structure and Cycle

Cardiac myocytes begin rapidly proliferating early in fetal life; during the perinatal period, proliferation stops. During the perinatal period of human development, cardiac myocytes undergo a second round of DNA synthesis and nuclear mitosis without cytokinesis. This leaves the majority of cardiac myocytes binucleated. Adult cardiac myocytes do not reenter the cell cycle when exposed to growth signals. Thus, the only means for cardiac mass enlargement is through an increase in cell size or hypertrophy. The failure of adult cardiac myocytes to reenter the cell cycle significantly limits their potential for self-renewal or repair after injury such as a myocardial infarction. An intensive field of research is whether other progenitor or stem cells can be signaled to differentiate into cardiac myocytes in order for repair to occur after significant injuries.

The heart is the pump to the vascular system. The left ventricle has an ellipsoid shape with the long axis directed from apex to base. The left ventricle's shape is the ideal geometry to pump blood into the higher pressure systemic vascular system. The efficient function of this pump is dependent on the integrity and coordination of the anatomic components of the four-chambered heart through the cardiac cycle as illustrated in ◘ Fig. 14.1. The cardiac cycle is divided into ventricular contraction (systole) and ventricular relaxation (diastole). Throughout the cardiac cycle, oxygen-depleted blood returns to the right atrium while oxygen-rich blood returns to the left atrium. The returning blood results in a pressure rise in the atria and venous system referred to as the *v* wave. Once ventricular pressure falls below the atrial pressure during diastole, the right-sided three-leaflet tricuspid valve and left-sided two-leaflet mitral valve (atrioventricular or AV valves) open, and blood enters the respective ventricles; atrial pressure begins to fall as the ventricles rapidly fill. Toward the end of diastole, atrial contraction (seen as the *a* wave on atrial pressure monitoring) occurs propelling an additional volume of blood into the ventricles while producing a rise in atrial and venous pressure. Because there are no valves between the venous system and the atria, the right atrial waves can also be seen in the venous system. Under normal conditions, atrial contraction contributes less than 20% of ventricular filling but can have a more significant contribution when diastolic filling time decreases as heart rate rises or when ventricular walls are stiff and thickened, which is most often due to hypertrophy.

Dysrhythmias disrupt the cardiac cycle resulting in uncoordinated anatomic and contraction function. For example, a venous "cannon" *a* wave can be appreciated when atrial contraction occurs against a closed AV valve due to dyssynchrony between the atrium and ventricles.

After atrial contraction, filling is complete, and the ventricle contains an end-diastolic volume (EDV) of blood with a resultant end-diastolic pressure (EDP). Clinically, the EDV represents the patient's intravascular volume status or preload and impacts the contractile nature of the myocardium illustrated by Starling's law (◘ Fig. 14.2). The QRS complex marks the beginning of ventricular depolarization/contraction and the start of systole. As ventricular contraction proceeds, pressure in the ventricles exceeds that of the atria, closing the AV valves and producing the first heart sound, S_1 (◘ Fig. 14.1). AV valves are anchored to the ventricles via chordae tendineae and papillary muscles that prevent valvular inversion into the atria. Competency of the AV and outflow tract valves allows ventricular isovolemic contraction to occur. The bowing of

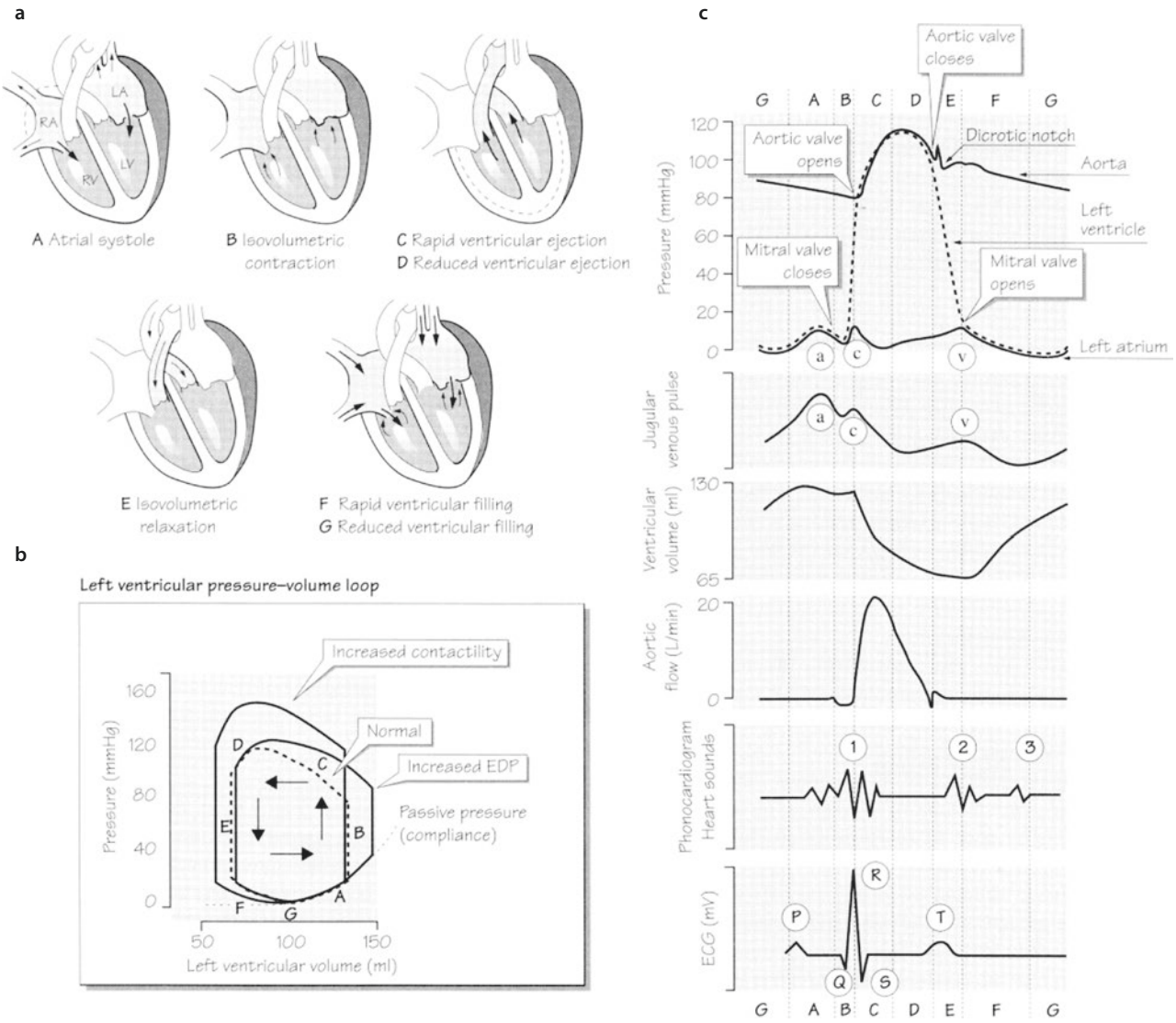


Fig. 14.1 Elements of a complete cardiac cycle: anatomic sequence **a**; left ventricular pressure-volume loop **b**; time-correlated left atrial, left ventricular, aortic, and venous pressures; ventricular volume; aortic flow; heart sounds; and electrocardiogram, through the cardiac cycle **c**. (From Aaronson et al. (2004))

the AV valves from the pressure generated during ventricular contraction results in an atrial and venous *c* pressure wave. When pressure in the ventricles exceeds the diastolic pressure in the aorta and pulmonary artery, the outflow valves are forced open and blood is ejected. Once ventricular contraction stops and repolarization begins, marked by the appearance of the electrical T-wave, pressure in the ventricle falls below that of the aorta and pulmonary artery, closing the aortic and pulmonary valves, producing the aortic A_2 and pulmonary P_2 components of the second heart sound (S_2). With closure of the aortic valve, pressure in the aorta briefly increases resulting in the aortic dicrotic notch pressure wave. The volume of blood ejected during one heartbeat is the stroke volume (SV); the ejection fraction is the proportion of EDV blood ejected, or SV/EDV, and is often used to estimate heart function. Once the outflow valves close, diastole begins again. The ventricles enter into isovolemic relaxation while the atria continue filling. The right atrium fills with caval

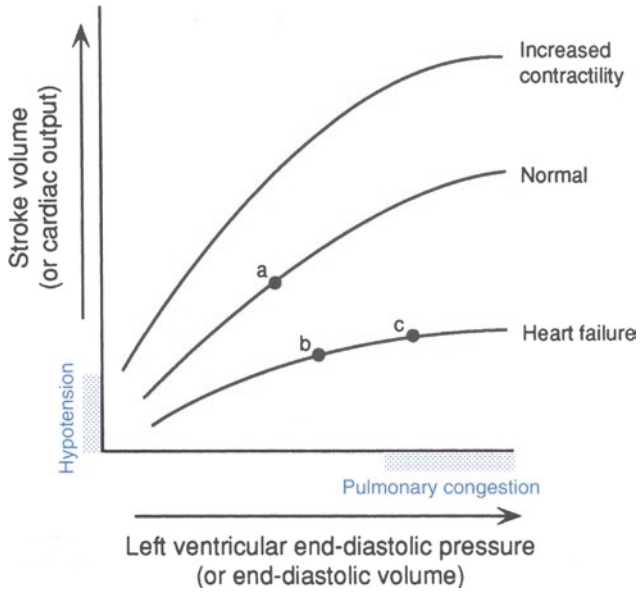


Fig. 14.2 Frank-Starling curves. Left ventricular (LV) performance curves relate preload, measured as LV end-diastolic volume (EDV) or pressure (EDP), to cardiac performance, measured as ventricular stroke volume or cardiac output. On the curve of a normal individual (*middle line*), cardiac performance continuously increases as a function of preload. States of increased contractility (e.g., norepinephrine infusion) are characterized by an augmented stroke volume at any level of preload (*upper line*). Conversely, decreased LV contractility (commonly associated with heart failure) is characterized by a curve that is shifted downward (*lower line*)

venous blood while the left atrium fills with pulmonary venous return. The *v* central venous pressure wave is produced during atrial venous filling against the closed AV valves. When atrial pressure exceeds ventricular pressure, the AV valves open and ventricular filling begins (Fig. 14.1).

The cardiac cycle also impacts oxygen delivery to the myocardium via the right and left coronary arteries originating from the aortic root. Blood flow (Q) into the coronaries is proportional to aortic diastolic pressure and inversely related to resistance (Q = P/R). During systole, small coronary branches are compressed by the contracting myocardium increasing resistance and limiting flow, leaving the majority of coronary blood flow to occur during diastole. Coronary blood flow is therefore affected by changes in aortic diastolic pressure and diastolic filling time. The majority of coronary venous blood returns to the heart via the coronary sinus into the right atrium. The coronary perfusion gradient across the myocardium can be thought of as the difference between the aortic diastolic pressure and the right atrial pressure or EDP of the left ventricle, whichever is higher.

Myocardial perfusion gradient between the aortic diastolic pressure and the right atrial or left ventricle end-diastolic pressure (LVEDP) becomes an important factor when respectively treating patients with high atrial pressures, such as patients with Fontan physiology or patients with reduced cardiac pumping function that leads to an elevated LVEDP.

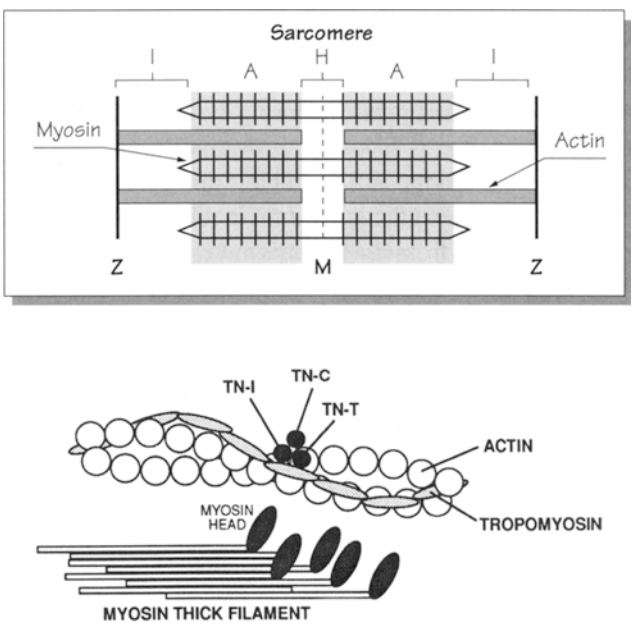
The heart resides in the pericardial sac that is made up of a fibrous outer layer and an inner serosal layer. The serosal layer lines the external surface of the heart muscle forming the visceral pericardium and then folds back onto itself to line the outer fibrous layer forming the parietal pericardium. The space between the visceral and parietal pericardium contains a small amount of fluid to reduce friction between the layers generated during the cardiac cycle. Restrictive disease affecting the pericardium or excess pericardial fluid can adversely affect cardiac filling and function during various portions of the cardiac cycle. Furthermore, the parietal pericardium attaches to the diaphragm. Thus, in settings with a flattened diaphragm, such as severe asthma or bronchiolitis or excessive positive pressure ventilation, the heart is compressed impairing venous filling.

The "heart" image on chest X-ray should always be referred to as a cardiac shadow or silhouette. The concept of a cardiac shadow allows for including pericardial pathology in the differential diagnosis of an enlarged silhouette.

14.2.2 Myocardial Contraction: Cellular Components

The cardiac cycle is dependent on sequences of myocardial contraction and relaxation. The cardiac myocyte is a highly specialized cell that contains substructures that enable this ongoing contraction-relaxation cycle.

Surrounded by sarcoplasmic reticulum, cytoplasm, and mitochondria are bundles (fibrils) that comprise the contractile apparatus. Fibrils are made up of individual sarcomeres that contain the basic myofibrillar contractile units: actin, tropomyosin, troponin, and thick myosin filaments. Actin is the thin filament attached to the sarcomere at the Z-line which interdigitates between the myosin components (◘ Fig. 14.3). The muscle flexes when the myosin heads attach to and "pull" on the actin filaments in an ATP-dependent process, sliding the components past each other. Tropomyosin resides between the grooves of the actin filaments. Troponin is a three-subunit regulator protein consisting of troponin T (TN-T) that acts to attach actin and tropomyosin filaments, troponin C (TN-C) that acts as a calcium binding site, and troponin I (TN-I) that acts to inhibit the ATPase responsible for the actin-myosin interaction. Under the influence of calcium, troponin functions as the "on-off" switch for myocardial cell contraction. An increase in cytosolic calcium concentration enables the interaction of cardiac myosin and actin filaments, whereas a decrease in cytosolic calcium concentration inhibits actin-myosin interaction. During relaxation, actin-myosin binding is inhibited by troponin I and tropomyosin. When intracellular calcium levels rise, calcium is available to bind to TN-C. Calcium binding to TN-C blocks TN-I's inhibitory effect on tropomyosin, thus allowing tropomyosin and troponin to undergo conformational changes that are conducive to actin-myosin cross bridging. Contraction continues until intracellular calcium levels are reduced by calcium uptake into the sarcoplasmic reticulum, freeing TN-C of calcium with subsequent inhibition of the actin-myosin interaction and relaxation of the myocardial muscle (◘ Fig. 14.3). A number of protein regulators in the myofilament regulate the interaction of actin and myosin. Mutations of one of these protein regulators, cardiac myosin-binding protein C, are responsible for the disease hypertrophic cardiomyopathy.



◘ **Fig. 14.3** Muscle element structures and interaction: (*Top*) sarcomere unit; A band (A), H zone (H), I band (I), M line (M), and Z disc (Z). (*Bottom*) Schematic diagram of the main contractile proteins of the myocyte, actin, and myosin. Tropomyosin and troponin (components TN-I, TN-C, and TN-T) are regulatory proteins

The electrical activity of the heart initiates the cardiac cycle. At the cellular level, "excitation-contraction" coupling relates depolarization of the heart to cellular calcium flux and the cellular contraction-relaxation sequence (◘ Fig. 14.4). The intracellular membranous sarcoplasmic reticulum (SR) is largely responsible for both the increase in cytoplasmic calcium concentrations required for contraction and the removal of calcium allowing for relaxation. During phase two of cellular depolarization, calcium enters the cell via L-type voltage-gated calcium channels within the cell membrane (sarcolemma); however, the rise in calcium concentration is not great enough to trigger muscle contraction. Instead, the initial cellular increase in calcium triggers a larger release of calcium stored in the SR via ryanodine receptors – "calcium-induced calcium release." With the large increase in intracellular calcium, calcium binds to the TN-C subunit of troponin, changing the configuration of tropomyosin and allowing the actin and myosin elements to initiate contraction. Contraction will continue as long as there is calcium available to bind TN-C and ATP to fuel the process. As the cell electrically repolarizes, the cell membrane calcium channels close. Calcium is actively sequestered back into the SR via an ATPase-dependent pump; calcium is also extruded from the cell by a sodium-calcium exchanger and to some degree by an active calcium ATPase-dependent pump residing in the cell membrane. Once calcium is no longer available to bind to TN-C, tropomyosin again inhibits the interaction of actin and myosin, reestablishing relaxation and diastole.

Given the importance of calcium ions in myocardial contraction and relaxation, it is not surprising that most inotropic agents, both positively and negatively affecting the heart, mediate their effects via impacting calcium flux within the cardiac cell. G protein-coupled receptors often mediate the effects of different cardiac inotropes through activation of a second messenger system that affects calcium ion flux. Infusions of calcium salts can act as a potent inotrope, particularly in neonates due to the dependence of the neonatal heart on transcellular calcium flux. Specifics regarding various clinical inotropes are discussed in ▶ Chap. 17, Cardiovascular Drug Therapy. Plasma-ionized calcium concentrations have a direct effect on myocardial contraction; low ionized calcium concentrations have a negative inotropic effect, while raising plasma-ionized calcium concentrations positively influences contraction but can also increase afterload by stimulating vascular smooth muscle contraction. Acidosis exerts a direct negative inotropic effect in general, but acidosis stimulates endogenous sympathetic nervous system activity that can counteract this effect. Acidosis also has the property of increasing plasma-ionized calcium concentrations, shifting the equilibrium between protein-bound calcium and free calcium, which potentially increases inotropic activity. Critically ill patients may present with both acidosis and ionized hypocalcemia as part of their illness. Furthermore, infusions of albumin or blood products can transiently lower ionized calcium concentration due to calcium binding with albumin or citrate, respectively. Therefore, it is important that clinicians identify and correct low ionized calcium concentrations prior to or in concert with attempting pharmacologic correction of acidosis.

Correction of acidosis is often best left to the patient as the clinicians address the cause. A mild to moderate acidotic environment can be beneficial, allowing for a higher ionized calcium concentration and ease of unloading oxygen to tissue from hemoglobin (left shift of oxyhemoglobin dissociation curve).

14.2.3 Cardiac Pump Function

Cardiac output (CO) is the measure of blood volume per unit time delivered to the body and is the product of stroke volume (volume of blood pumped per heartbeat in milliliters) and heart rate (beats per minute). Stroke volume is determined by the following: *preload*, the amount of blood in the heart affecting myocardial fiber stretch prior to contraction; *afterload*, the forces opposing the ejection of blood from the ventricles; *contractility*, the strength of myocar-

Heart rate is a valuable marker for cardiovascular integrity in newborns and young children. Stroke volume is largely fixed in neonates, which results in the need to increase heart rate to increase CO in this population.

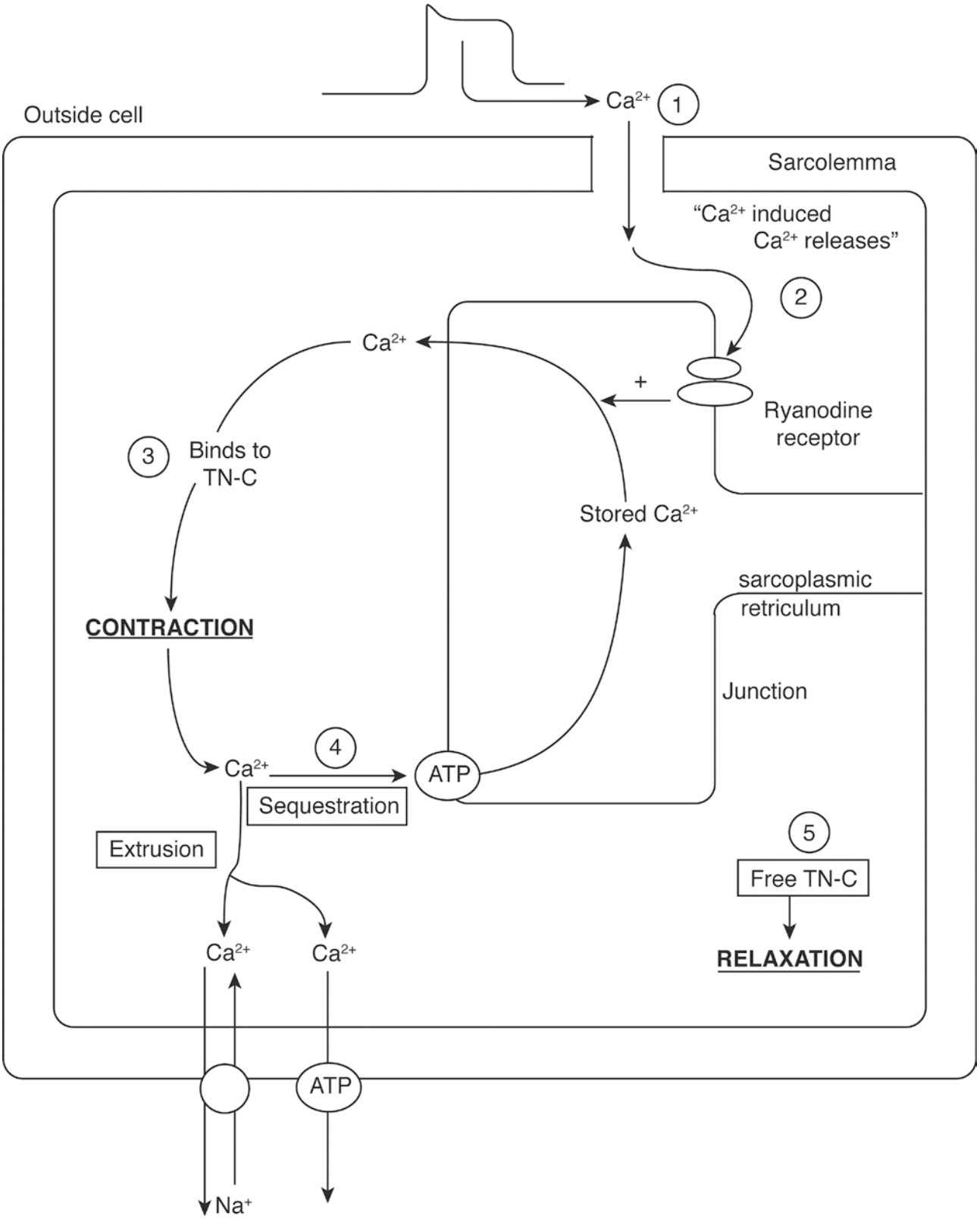


Fig. 14.4 Cellular cardiac cycle: (1) Myocardial depolarization opens L-type calcium channels in the sarcolemma allowing calcium to enter the cell. (2) Rising calcium concentrations trigger an even greater release of calcium from calcium stores within the cell via ryanodine receptors on the sarcoplasmic reticulum (SR) – "calcium-induced calcium release." (3) Calcium concentrations are now high enough to bind to troponin, allowing actin and myosin to interact and muscle contraction to occur. (4) Cellular repolarization triggers sequestration of calcium back into the SR and extrusion of calcium out of the cell, lowering intracellular calcium concentrations. (5) Falling intracellular calcium concentrations free tropomyosin to once again inhibit actin and myosin interaction leading to myocardial relaxation

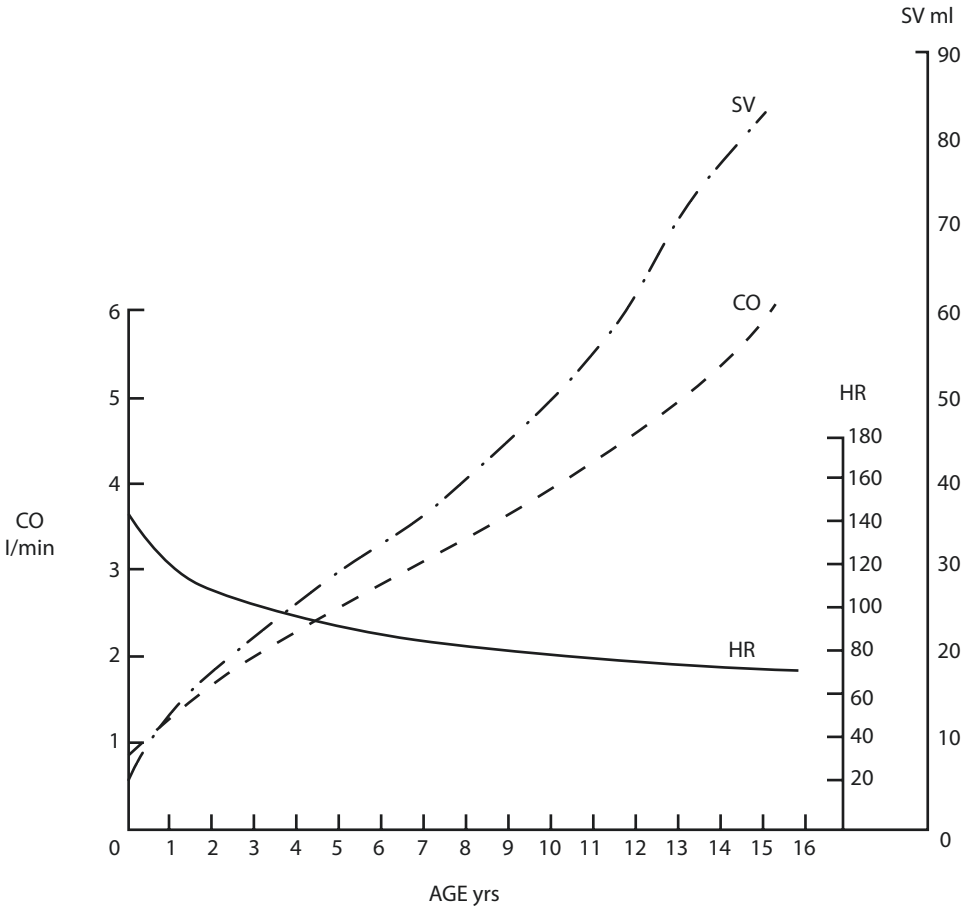


Fig. 14.5 Changes in cardiac output (*CO*), stroke volume (*SV*), and heart rate (*HR*) with age

dial contraction independent of preload and afterload; and *lusitropy*, the rate of myocardial relaxation. As the body grows, cardiac output must increase to keep up with the body's increased absolute metabolic activity. The relative effect of stroke volume and heart rate as determinants of cardiac output shifts with advancing age; stroke volume increases with age accounting for most of the absolute increase in cardiac output as an individual gets older while heart rate decreases (Fig. 14.5). The cardiac index (CI) is a measure of an individual's cardiac output (CO) adjusting for their size or body surface area (BSA); CI = CO/BSA. A normal CI is in the range of 2.5–4 L/min/m^2. Note that although absolute stroke volume and cardiac output increase with age, the stroke volume index and cardiac index decrease in older children and adults compared with infants and young children.

14.2.4 Stroke Volume: Preload

Otto Frank in the late 1800s and E. H. Starling in the early 1900s both noted that stroke volume increased as the pre-contraction cardiac muscle fiber length was increased. Muscle fibers exposed to a "load" prior to, or "pre," contraction lengthen and allow for an increased number of actin-myosin interactions during contraction, generating a stronger force. The stretching of the cardiac muscle is equated with end-diastolic ventricular volume; the greater the end-diastolic volume, the greater the stretch and resultant increase in ejected stroke volume during systole. The relationship between stroke volume and end-diastolic volume is known as the Frank-Starling ventricular function curve (Fig. 14.2).

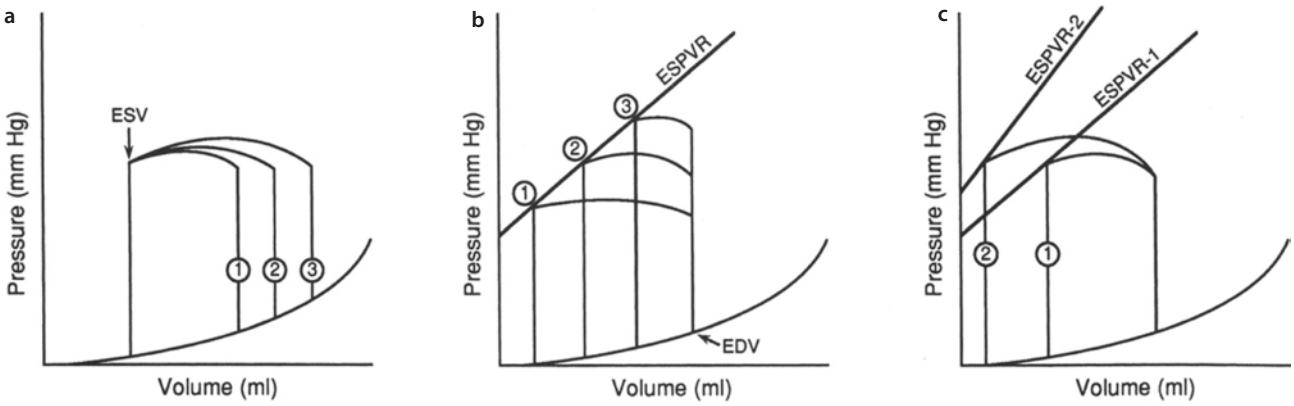


Fig. 14.6 The effect of varying preload, afterload, and contractility on the pressure-volume loop. **a** When arterial pressure (afterload) and contractility are held constant, sequential increases (*lines 1*, *2*, *3*) in preload (measured in this case as end-diastolic volume (*EDV*)) are associated with loops that have progressively higher stroke volumes but a constant end-systolic volume (*ESV*). **b** When preload (*EDV*) and contractility are held constant, sequential increases (*points 1*, *2*, *3*) in afterload (which increases arterial pressure) are associated with loops that have progressively lower stroke volumes and higher end-systolic volumes. There is a nearly linear relationship between the afterload and the ESV, termed the end-systolic pressure-volume relation (*ESPVR*); the slope of this curve defines the contractile state of the heart. **c** A positive inotropic intervention shifts the end-systolic pressure-volume relation upward and leftward from ESPVR-1 to ESPVR-2, resulting in loop 2, which has a larger stroke volume and smaller end-systolic volume than the original loop 1. (From Lilly (2003))

End-diastolic pressure is often used as equivalent to end-diastolic volume because it is easier to measure but can be misleading under a number of situations, such as when the compliance of the ventricle is poor, venous compliance is increased, or when the cardiovascular system is exposed to increased intrathoracic pressure. The effects of increasing preload on stroke volume while holding afterload and contractility constant can also be depicted in a pressure-volume loop diagram (Fig. 14.6a). As end-diastolic volume is increased, the heart ejects larger stroke volumes, always returning to the same end-systolic starting volume. The opposite effect on stroke volume is observed when preload is decreased and explains the decrease in stroke volume in conditions associated with hypovolemia or increased vascular capacitance where preload is reduced.

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14.2.5 Stroke Volume: Afterload

Afterload is the force the ventricle has to overcome to eject blood into the systemic or pulmonary systems. From a cellular perspective, afterload is the sum of the forces against which cardiac fibers must shorten during systole. Factors affecting afterload include vascular pressure, vascular resistance, intrapleural pressure, and blood viscosity; clinically, afterload is often related to the systemic or pulmonary vascular resistance. As afterload is increased, muscle shortening and the velocity of contraction decreases, resulting in less blood ejected during each cardiac cycle when preload and contractility are held constant. The effects of increasing afterload on stroke volume are shown in Fig. 14.6b; as afterload is increased, end-systolic pressure rises along with end-systolic volume, resulting in a smaller stroke volume. Clinically, contractility and preload are not constant. Thus, as afterload (typically resistance) increases in a patient with normal cardiac function, stroke volume is often maintained by a normally functioning ventricle, but at the cost of arterial hypertension (SV α P/R).

The systemic aortic blood pressure and pulmonary artery pressure are often used as references for left and right ventricular afterload, respectively.

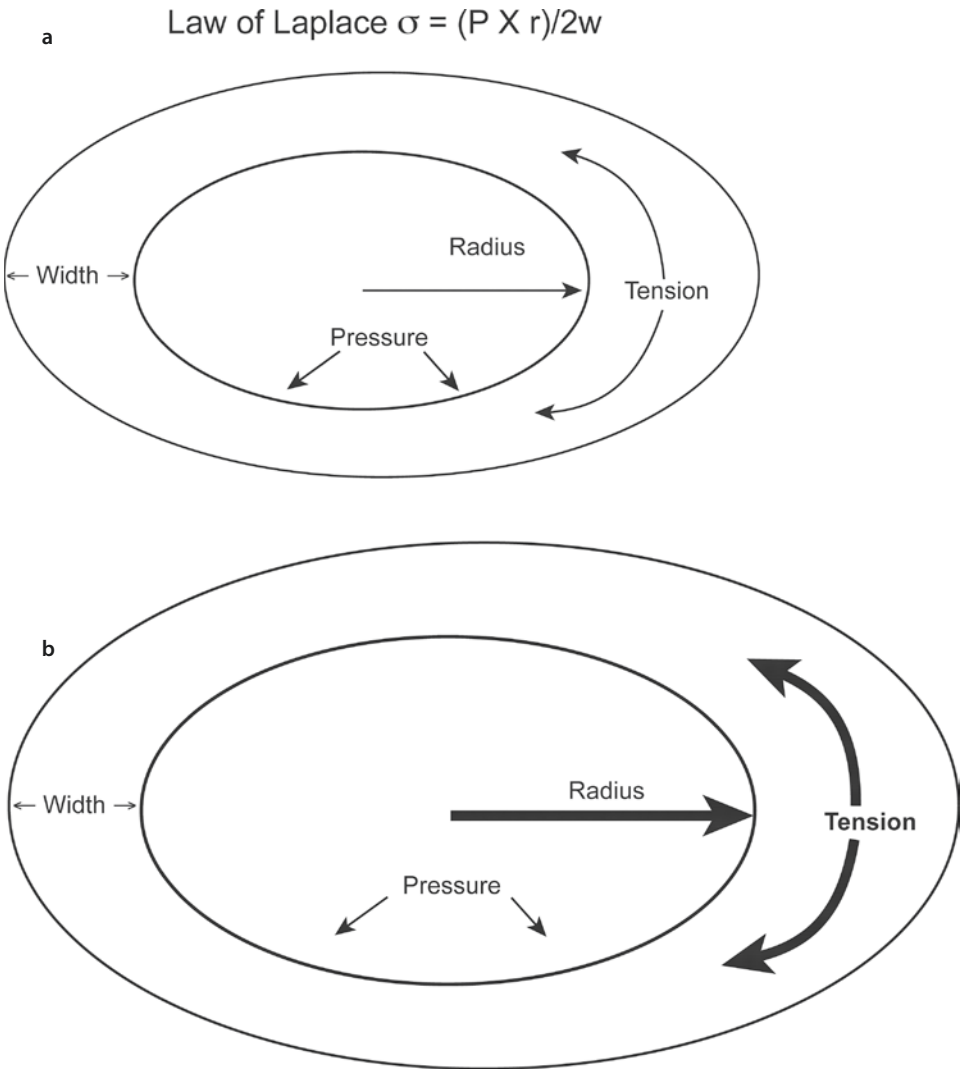

Fig. 14.7 Law of Laplace: T = (P × r)/2w, where *T* is wall stress or tension, *P* is pressure, *r* is radius, and *w* is wall thickness. **a** Normal left ventricular radius. **b** Effect of increasing ventricular radius on wall tension (afterload)

However, using pressures as an indicator of afterload can be misleading. Pressure is directly proportional to both flow (Q), or think of it as cardiac output, and resistance (R): P = QR. In the case of compensated shock, cardiac output may be decreased while resistance has increased by a similar amount, leading to a significant increase in afterload but little change in systemic pressure. The clinical signs indicating a compensated shock state tell the clinician more about the afterload on the heart than the blood pressure alone.

Afterload can also be expressed as ventricular wall tension during contraction, estimated using the law of Laplace for a sphere: T = (P × r)/2w, where T is wall stress or tension, P is ventricular transmural pressure, r is ventricular radius, and w is ventricular wall thickness (Fig. 14.7). Although the ventricle is not a perfect sphere and the law of Laplace is only an estimate of wall stress, the formula allows for a greater understanding of clinical cardiac conditions. According to Laplace's law, increasing the radius of the ventricle increases the wall tension needed to balance a given transmural ventricular pressure. As a result, increasing the forces (afterload) that resist ventricular wall shortening should lead to a decrease in stroke volume. Despite the effect of increasing radius on afterload, in the healthy heart, SV may actually increase because the positive effects of increasing fiber length (preload) are greater than the negative effects of increasing ventricular radius.

Healthy hearts are relatively preload dependent and afterload independent. Failing hearts tend to be relatively afterload dependent and preload independent. Thus, as afterload increases in the healthy heart, CO is maintained and blood pressure increases, whereas in the failing heart, blood pressure is maintained and CO falls as afterload increases.

In contrast, this relationship is altered in the failing myocardium when the ventricle is pathologically dilated (as in congestive heart failure or dilated cardiomyopathy). The myocardial fibers may be unable to generate enough force to overcome the effects of increasing ventricular radius (increased afterload), which leads to a progressive decline in ventricular performance despite adequate (or more than adequate) preload. Various causes of heart failure lead to ventricular dilatation, increasing the ventricular radius and increasing wall stress resulting in greater energy expenditure per stroke volume. Clinically, the use of diuretics (decrease ventricular radius and thus indirectly decrease afterload) and vasodilators (decrease systemic vascular resistance and thus directly decreasing afterload) are the mainstay in the treatment of the failing dilated myocardium. Conversely, ventricular hypertrophy can occur secondary to chronic increases in afterload such as with long-term hypertension; the increase in wall thickness leads to a decrease in wall stress but unfortunately can adversely affect ventricular compliance and end-diastolic relaxation and ultimately decrease stroke volume.

14.2.6 Stroke Volume: Contractility

Myocardial contractility relates to the ability of muscle to generate force and is independent of preload and afterload. As discussed earlier, the inotropic state of the myocardium is dependent on cellular calcium flux. The independence from preload is noted in the Frank-Starling curve; for a given EDV, SV increases as contractility increases, which may reflect the effect of positive inotropic agents (see ▶ Chap. 17, Cardiovascular Drug Therapy) or endogenous hormonal catecholamine influences such as epinephrine. The curve is depressed in a negative inotropic environment such as in congestive heart failure. The effects of increasing contractility on stroke volume can also be demonstrated in the pressure-volume loop diagram (◘ Fig. 14.6c).

14.2.7 Stroke Volume: Lusitropy

Lusitropy refers to the rate of myocardial relaxation. Myocardial relaxation is not simply a passive process of elastic recoil of the muscle fibers but rather an active process involving the movement of calcium ions across membranes. Cardiac lusitropy is influenced by a number of factors including the thickness of the ventricular wall, ventricular wall composition (healthy muscle vs. pathologic fibrosis or amyloid), elastic recoil, sympathetic stimulation, loading conditions, and mechanical interaction with the pericardium. In the healthy myocardium, relaxation is load dependent. An increase in systolic pressure slows the myocardial relaxation rate. An increase in heart rate shortens the duration of the cardiac myocyte action potential and accelerates myocardial relaxation. A negative change in lusitropy typically results in reduced diastolic distensibility in most cases. Diastolic dysfunction can lead to or exacerbate preexisting heart failure in three ways: increasing cardiac filling pressures, reducing cardiac output at rest due to reduced stroke volume, and limiting the augmentation of cardiac output during exertion. Diastolic dysfunction can lead to pulmonary edema secondary to left atrial hypertension from elevated cardiac filling pressures and endocardial ischemia due to impaired coronary perfusion.

14.3 Cardiopulmonary Interactions

Caring for critically ill children requires a thorough knowledge of heart-lung interactions, how critical illness can alter these interactions, and finally how therapeutic interventions in the intensive care unit can affect cardiopulmonary function.

Cardiopulmonary interactions in the healthy patient with normal function of the heart and lungs are subtle and typically go unrecognized. Examples of these interactions include normal variations in systolic blood pressure and heart rate during spontaneous respiration. Even the use of positive pressure ventilation (PPV) and exaggerated spontaneous respiratory efforts do not typically cause cardiovascular compromise in the patient with normal cardiac and pulmonary function. However, the use of PPV for respiratory failure may impair cardiovascular system function. It is important to emphasize that mean airway pressure, which directly influences mean intrathoracic pressure, is the key variable affecting cardiopulmonary interactions during PPV. Other phasic changes in airway pressure have generally minor effects. Decreased cardiac output is a recognized consequence of increased mean airway pressure resulting from the use of positive end-expiratory pressure (PEEP) during the treatment for respiratory failure and during recruitment maneuvers. Extremely negative pleural pressures, as seen during airway obstruction and asthma exacerbations, may also compromise cardiac output. Conversely, the use of PPV can improve cardiac output in patients with left ventricular dysfunction, whereas weaning from PPV can improve cardiac output in patients with right heart failure.

The physical approximation of the heart and lungs within the thoracic cavity, the placement of the pulmonary vasculature in series with the cardiac ventricles, and the extrathoracic systemic vascular bed provide the basis for heart-lung interactions (◘ Fig. 14.8). As a result of this unique physical layout, changes in intrathoracic pressure or lung volume may have opposite effects on the right (RV) and left ventricle (LV).

14.3.1 Neural Regulation of Cardiopulmonary Interactions

Increase in pulmonary blood flow during inspiration improves ventilation/perfusion matching.

The importance of neural mediation between heart and lung function is well recognized. One subtle cardiopulmonary interaction in the healthy individual is the rhythmic change in heart rate during the respiratory cycle. The increase in heart rate during inhalation and decrease in heart rate during exhalation, known as respiratory sinus arrhythmia, are controlled by input from the brain stem through the vagus nerve. Evidence exists that even this seemingly minor cardiopulmonary interaction has a physiologic role in improving cardiorespiratory function by matching perfusion with ventilation. The transient increase in alveolar ventilation during inspiration is matched by an increase in venous return, heart rate, and pulmonary blood flow. This matching of ventilation and perfusion decreases dead space ventilation and intrapulmonary shunting, thus improving gas exchange. Respiratory sinus arrhythmia is a simple yet physiologically significant example of cardiorespiratory interactions that occur during spontaneous respiration. Respiration also affects autonomic regulation of vascular tone. For example, apnea results in decreased heart rate and increased systemic vascular resistance due to vagal and sympathetic influences. This "diving reflex" serves to maintain perfusion to the brain and heart while decreasing myocardial oxygen consumption.

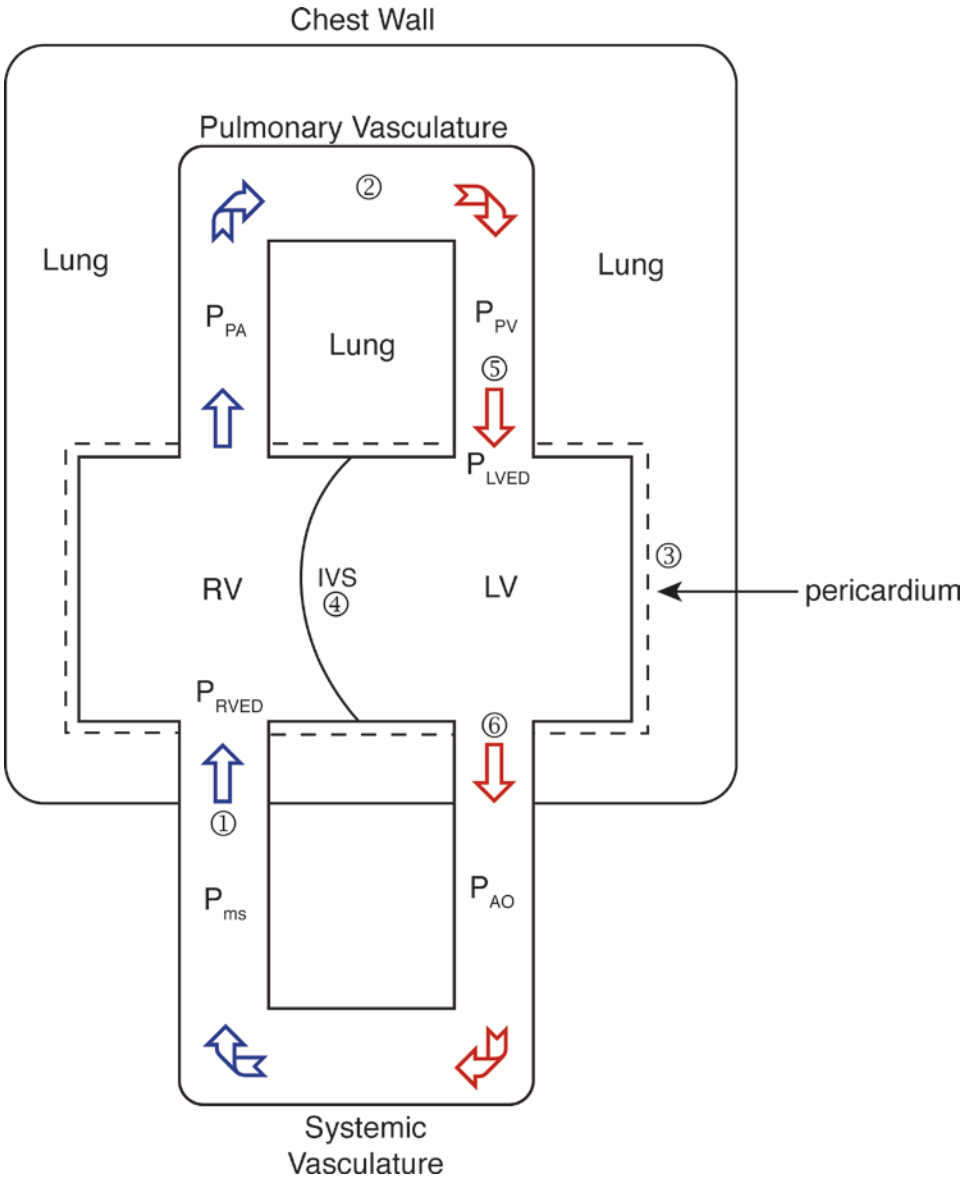

Fig. 14.8 Schematic figure showing the relationship between cardiovascular and pulmonary structures that affect cardiopulmonary interactions. The important relationships include those between (*1*) the mean systemic venous pressure (P_{ms}) and right ventricular end-diastolic pressure (P_{RVED}), (2) lung volume and pulmonary vascular resistance, (3) the cardiac fossa restricted by the pericardium and lungs, (4) the interventricular septum (*IVS*) shared by the right (*RV*) and left ventricle (*LV*), (5) the effect of intrathoracic pressure (*ITP*) and lung volumes on pulmonary venous capacitance and LV filling, (6) and the effect of ITP on LV afterload. P_{PA} pulmonary artery pressure, P_{PV} pulmonary vein pressure, P_{LVED} LV end-diastolic pressure, P_{AO} arterial pressure

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14.3.2 Intrathoracic Pressure Changes During Respiration

Fundamental to understanding cardiopulmonary interactions are the pressure and volume changes that occur in the various intrathoracic compartments during respiration. It is primarily the transmural wall pressure and lung volume surrounding the heart and pulmonary vasculature that are ultimately responsible for alterations in cardiac function during respiration. Spontaneous respiration produces negative (subatmospheric) intrapleural pressures, whereas mechanical ventilation transmits positive pressure to the airways and thorax.

The intrathoracic pressures that are generated with respiration are distributed unequally throughout the airways and thorax due to gravitational forces, regional differences in elastic properties of the lung, and the fibrous structure of the pericardium. Gravitational forces on the lung and mediastinal structures create a pressure gradient within the esophagus and the pleural space that is

position dependent. During spontaneous respiration and PPV in the upright position, the pressure in the pleural space at the apex of the lung is less than at the base of the lung. In addition, regional differences in pleural pressure independent of gravitational forces exist and are likely due to regional differences in elastic properties of the lung and chest wall. However, the use of high positive airway pressures abolishes the gravitational gradient and reduces regional differences in pleural pressure.

Transmission of intrathoracic pressures to the pericardial space is variable due to regional elastic properties in the lung and pericardium, gravitational forces, intravascular volume, and changes in lung compliance.

Ultimately, the forces acting on the external muscular wall of the heart and vasculature are those that are most relevant to the clinician considering heart-lung interactions, but they are also the most difficult to measure. Correlation between pressures measured in the airway, esophagus, pleural space, and pericardial space can vary significantly. Elastic properties of the lung and fibrous pericardium likely contribute to the pressure difference within these spaces. Although the qualitative changes in pressure measured at different locations within the thorax during respiration correlate with respect to the positive or negative direction of the change, the quantity of pressure change within the various intrathoracic spaces can be quite variable. Pressures generated in the airway or pleural spaces are attenuated prior to reaching the pericardial space. Epicardial pressures are also influenced by intravascular blood volume as well as surrounding extrapericardial pressures. Intravascular volume loading increases pericardial surface pressure and decreases the influence of respiration on pericardial pressure. Esophageal and pleural pressures tend to underestimate the pressures within the pericardial space when ventricular volumes are increased. Therefore, using a surrogate pressure, such as esophageal or airway, for pericardial pressures to calculate vascular transmural wall pressure is potentially inaccurate.

Changes in thoracic wall and lung compliance also alter the transmission of intrathoracic pressures to the external cardiac surface. In respiratory failure requiring mechanical ventilation, transpulmonary pressure increases as compliance of the respiratory system decreases and airway pressures generated by PPV are attenuated before they reach cardiovascular structures. To maintain lung volumes for adequate gas exchange, however, higher airway pressures may be required, resulting in elevated pleural and pericardial pressures that may contribute to hemodynamic compromise.

14.3.3 The Effect of Respiration on Cardiac Function

Spontaneous respiration with negative (subatmospheric) pressure ventilation may improve cardiac output in children with RV dysfunction.

Depending on the underlying cardiac and hemodynamic condition of the patient, cardiac function can be affected in a positive or negative manner during respiration. During spontaneous inspiration with subatmospheric intrathoracic pressures, RV output increases due to increased venous return, whereas LV output decreases due to dilation of intrapulmonary veins. Therefore, spontaneous breathing with negative pressure ventilation may improve cardiac output in children with RV dysfunction. Conversely, during the inspiratory phase of PPV, RV output decreases and LV output initially increases. Although PPV has favorable effects on LV afterload, using high levels of PPV has been associated with a decrease in LV stroke volume and cardiac output. The mechanisms responsible for the decrease in cardiac output during PPV include a decrease in systemic venous return, an increase in RV afterload, decrease in LV preload, and a decrease in ventricular contractility.

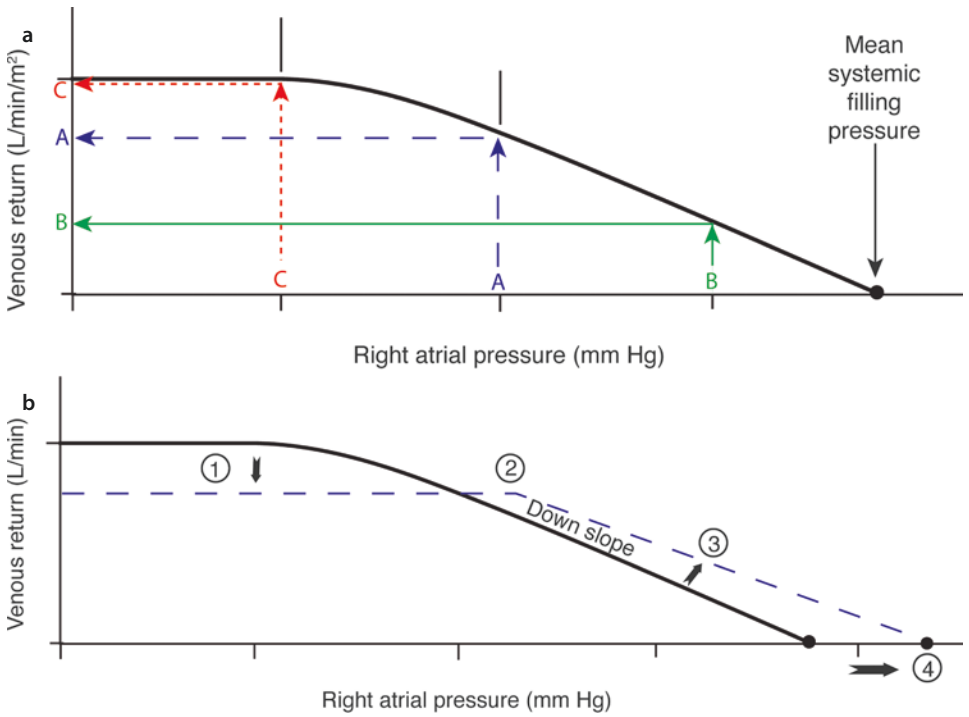
14.3.4 Right Ventricular Preload/Systemic Venous Return

Spontaneous respiration increases venous return by decreasing P_{RA} and increasing the pressure gradient between the systemic veins and the right atrium.

Venous return is limited by collapse of extrathoracic blood vessels when P_{RA} is less than 0 mm Hg.

PPV decreases venous return by increasing P_{RA} and reducing the pressure gradient between systemic veins and the right atrium.

The influence that respiration has on venous blood returning to the heart is arguably the most important clinical effect of breathing on cardiac output. Although transient differences between venous return to the right heart and output from the left heart can occur, in steady-state conditions, LV output must be equal to venous return. Since Guyton performed his studies on venous return in dogs and applied his findings to humans, many investigators have studied the effect of respiration on venous return to the heart. Respiratory changes in intrathoracic pressure primarily alter venous return by changing right atrial pressure (P_{RA}) and shifting the intercept of P_{RA} on the venous return curve (◘ Fig. 14.9a). Subatmospheric intrathoracic pressures generated during spontaneous respiration decrease P_{RA} and increase the pressure gradient between systemic veins and the right atrium, resulting in an increased systemic venous return and thus pulmonary blood flow. Collapse of extrathoracic blood vessels limits the effect of subatmospheric intrathoracic pressure on venous return, which becomes maximum when right atrial pressure is below 0 mm Hg. Decreasing right atrial pressure below the upper inflection point on the venous return curve will not increase venous return but may have deleterious effects on cardiac function by increasing LV afterload (discussed below). The clinical importance of the plateau in venous return is recognizing that weaning from PPV (invasive or noninvasive) and transitioning to spontaneous (negative) pressure ventilation (NPV) may increase cardiac output but is limited by the



◘ **Fig. 14.9** **a** Effect of changing right atrial pressure (P_{RA}) on venous return. Baseline P_{RA} and venous return are represented by A. As P_{RA} increases from A to B, the intercept on the venous return curve shifts and results in lower venous return. Venous return is zero when P_{RA} equals mean systemic filling pressure. During spontaneous inspiration with an obstructed airway (Muller maneuver), P_{RA} decreases from A to C, and the intercept on the venous return curve shifts left and increases venous return. The effect of decreasing P_{RA} on venous return is limited by the plateau on the venous return curve, caused by collapse of the extrathoracic blood vessels. **b** The effect of positive end-expiratory pressure (PEEP) on the venous return curve. The application of PEEP in an animal model affected the venous return curve by (1) decreasing the maximum venous return (plateau), (2) shifting the inflection point of the venous return curve to the right, (3) altering the slope of the curve (1/resistance), and (4) increasing the zero flow intercept of the curve. These changes in the venous return curve help maintain venous return at higher right atrial pressures during PPV. (From Fessler et al. (1992))

collapse of extrathoracic blood vessels. Transmission of airway pressure to the right atrium during PPV decreases the pressure gradient between the "upstream" systemic venous vasculature and "downstream" right atrium, resulting in decreased venous return. This effect increases with increasing airway pressure until the right atrial pressure is equal to the mean systemic filling pressure (the pressure of the entire systemic circulation if blood flow were to be transiently stopped), at which point the absence of a pressure gradient prevents venous blood from returning to the heart.

Evidence suggests the effect of positive airway pressure on venous return is more complex than that described above. In an animal model, PEEP did not simply increase right atrial pressure and shift the intercept of the curve to the right; instead, it altered almost every aspect of the venous return curve (Fig. 14.9b). The effect of raising right atrial pressure during PPV is offset to some degree by an increase in upstream venous pressure and an alteration in the resistance to venous return, which helped maintain venous return to the right heart. This observation has been made by others and is attributed to the effects of respiration on vascular tone and splanchnic blood flow.

The influence of respiration on the systemic vasculature and the splanchnic vascular bed in particular is important to the discussion of venous return. Due to the large capacitance of the splanchnic vascular bed, its contribution to venous return is significant. During respiration, downward movement of the diaphragm into the closed abdomen increases intra-abdominal pressure and alters blood flow from both splanchnic and nonsplanchnic blood vessels through the IVC. The ultimate effect of respiration on IVC blood flow is determined by the patient's intravascular volume status and can be described using a model of vascular compartment "zones" analogous to the pulmonary vascular zones (Fig. 14.10). By isolating flow from splanchnic and nonsplanchnic sources of venous blood, animal studies have demonstrated how intravascular volume status affects the venous blood return through the IVC during diaphragm contraction. In hypervolemic animals with abdominal vascular zone

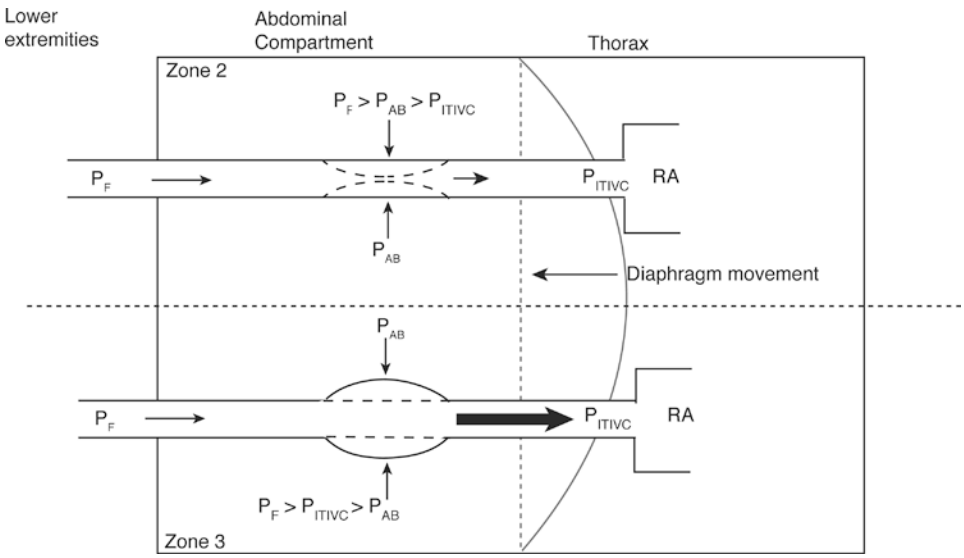


Fig. 14.10 The effect of respiration on inferior vena caval (IVC) blood flow using the vascular compartment zone model. In the upper panel modeling a Zone 2 condition (hypovolemic state), an increase in abdominal pressure during diaphragm descent increases splanchnic blood flow but creates a resistor and inhibits nonsplanchnic blood flow from the lower extremities. In the lower panel modeling Zone 3 conditions (hypervolemic state), an increase in abdominal pressure increases splanchnic blood flow. The increase in abdominal pressure does not create resistance to nonsplanchnic blood flow. *RA* right atrium, P_{AB} abdominal compartment pressure, P_F femoral venous pressure, P_{ITIVC} intrathoracic inferior vena cava pressure

III conditions, total IVC blood flow increased throughout contraction of the diaphragm due to an increase in splanchnic blood flow through the IVC. In hypovolemic animals with abdominal zone II conditions, IVC blood flow followed a biphasic pattern: initially increased with diaphragmatic contraction but subsequently decreased. The source of the initial increase in blood flow originates from splanchnic vessels. The later decrease in blood flow was caused by resistance to infrahepatic, nonsplanchnic blood flow. These studies provide convincing evidence that extrathoracic blood volume is an important component of cardiopulmonary interactions and serve to remind us that these interactions may be more correctly termed cardiovascular-pulmonary in nature. The importance of intravascular volume status during PPV is clear from studies using intravascular volume expansion during PPV, which have demonstrated that decreased cardiac output during PPV can be compensated for by intravascular volume infusion.

The healthy patient with adequate cardiopulmonary function and circulating blood volume will tolerate the effects of PPV on venous return with little or no compromise in cardiac output, likely through increased venous vascular tone, which decreases venous capacitance. However, there are circumstances (e.g., hypovolemic, septic, or hemorrhagic shock) when patients may not tolerate PPV, especially if high mean airway pressures are used in conjunction with hypovolemic states. In some circumstances, the reduction in cardiac output caused by PPV can be improved with intravascular volume expansion, which restores the pressure gradient between the systemic veins (i.e., the mean systemic filling pressure) and the right atrium. Although the amount of volume required to restore the pressure gradient is based on the patient's intravascular status and the mean airway pressure, clinical experience shows that 3–5 ml/kg is generally required. Subsequent boluses might be considered based on the patient's pathophysiology and physiologic response to the initial fluid challenge. In patients with cavopulmonary shunt physiology who are dependent on passive venous blood flow for pulmonary circulation, the use of any PPV may decrease cardiac output by decreasing systemic venous return. Therefore, patients with poor RV diastolic function or Fontan physiology may benefit from early weaning from PPV.

14.3.5 Right Ventricular Afterload

Both low and increased lung volumes contribute to increased pulmonary vascular resistance and RV afterload.

Since the RV and the pulmonary circulation, to which the RV delivers blood are both intrathoracic structures, they are affected by intrathoracic pressure changes in a similar manner. Therefore, the pressure difference between the internal and external ventricular wall, or transmural wall pressure, that directly affects LV afterload during respiration (discussed later) is not the primary respiratory determinant of RV afterload. Instead, the respiratory parameter most influential in determining RV afterload is lung volume.

During normal spontaneous respiration, the pulmonary vascular bed is a system with low pressure and resistance. Critical illness can increase pulmonary vascular resistance (PVR) through hypoxic vasoconstriction and the production of chemical mediators. In addition, mechanical forces may increase pulmonary vascular resistance through changes in lung volume. Optimizing lung volumes, matching ventilation with perfusion, reducing hypoxia and hypercapnia, and avoiding mechanical shear forces in the lung will minimize PVR and thus RV afterload. The mechanical effects of lung inflation during PPV can influence pulmonary vascular resistance via chemical mediators even after the cessation of lung stretch. The effect of active pulmonary vasocon-

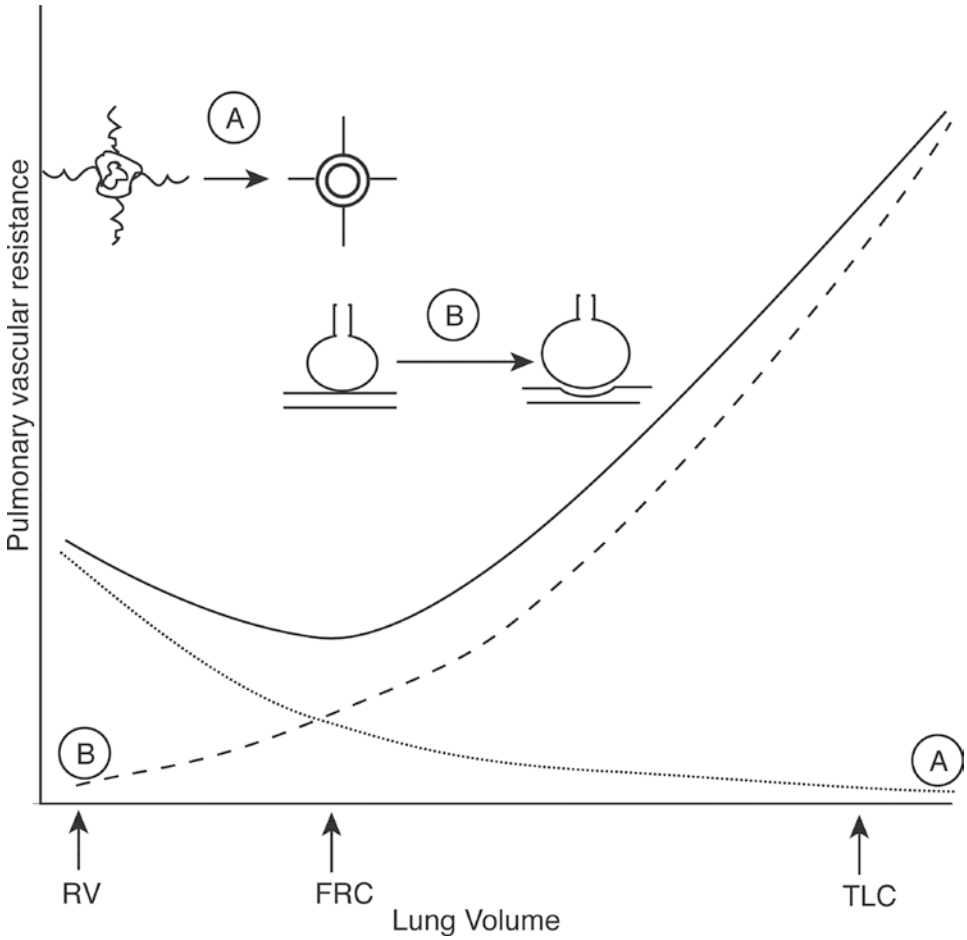


Fig. 14.11 Effect of lung volume on pulmonary vascular resistance. The effect of increasing lung volume on extra-alveolar vessels is shown in *inset and curve A* (••••). As lung volume increases, the extra-alveolar vessels are opened by mechanical forces and, in combination with the reversal of hypoxic vasoconstriction, reduce pulmonary vascular resistance. The effect of lung volume on alveolar capillaries is shown in *inset and curve B* (– – – –). As lung volume further increases, alveolar vessels are compressed and vascular resistance increases. The *solid line* combines the two vascular compartments and shows that deviations in lung volume either above or below *FRC* increase pulmonary vascular resistance and right ventricular afterload. *RV* residual volume, *FRC* functional residual capacity, *TLC* total lung capacity

striction from hypoxia, acidosis, and other chemical mediators is important to consider when discussing RV afterload. These mediators should be considered in cardiopulmonary interactions and are discussed in more detail elsewhere in this textbook. In the remainder of this section, we will review the mechanical forces that contribute to PVR and its effect on RV afterload.

Studies performed in isolated animal lungs provide the basis for our understanding of the relationship between PVR and lung volume. The relationship between lung volumes and PVR has been studied during inflation of the lungs from a collapsed state to full inflation. These studies identified several salient features of the relationship between lung volumes and PVR: (1) a slight decrease in PVR occurs as lungs are inflated from a collapsed state to a moderately inflated state, and (2) a significant increase in PVR occurs at high levels of lung inflation (Fig. 14.11).

The relationship between lung volume and PVR is present during both positive and negative pressure ventilations. The effect of lung volume on PVR is best understood if the pulmonary vascular bed is separated into two compartments: extra-alveolar vessels and vessels physically associated with alveoli. PVR is slightly increased when the lung is totally collapsed and decreases to its lowest point when the lung is inflated to functional residual capacity. The increased PVR noted at low lung volumes is attributed to a combination of hypoxic pulmonary vasoconstriction and collapse of extra-alveolar blood vessels. As the lung is inflated, the extra-alveolar vessels are held open by connective tissue that supports the vessel wall. Evidence for this phenomenon was found on microscopic examination of pulmonary vessel casts at various stages

PVR is lowest at lung volumes around FRC. PVR increases at low lung volumes due to hypoxic vasoconstriction and collapse of extra-alveolar vessels. PVR increases at high lung volumes due to alveolar distension that compresses alveolar capillaries.

of lung inflation, which demonstrated contortions and grooves in extra-alveolar small pulmonary vessels when the lung is collapsed. As lung volumes are increased above FRC, pulmonary vascular resistance increases as a result of the compression by distended alveoli of the alveolar capillary bed and decreased capillary blood volume.

PPV may be associated with an increased RV afterload in several clinical situations. The use of PEEP in patients with acute respiratory failure is associated with a decrease in right ventricular output. At low levels of PEEP, the decrease in RV output is a result of a decrease in systemic venous return, while at higher levels of PEEP, increased pulmonary vascular resistance also contributes to decreased RV output. Studies have shown that the effect of PEEP on RV function is dependent on the baseline function of the RV. Patients with baseline normal RV function did not have deterioration of RV function with the use of high levels of PEEP, while patients with RV dysfunction at baseline experienced a significant decline in RV function with the use of PEEP.

Typical tidal volume changes that occur around FRC with spontaneous respiration have minimal effect on PVR.

Typical tidal volume changes that occur around FRC with spontaneous respiration have minimal effect on PVR. The increase in PVR associated with atelectasis or moderate hyperinflation is unlikely to cause a clinically significant decrease in RV function or output in patients with normal RV function, while the patient with RV dysfunction may benefit from optimizing lung volume. Clinical experience in patients after Fontan procedures shows that even in the absence of the active RV pump, cardiac output can be maintained by optimizing lung volume and minimizing PVR. Therefore, optimizing lung volume to restore functional residual capacity will decrease PVR and improve RV output in patients with any of the following: RV dysfunction, cavopulmonary shunts, or neuromuscular disease or respiratory muscle fatigue associated with atelectasis or lung overdistension. Although optimizing lung volume around functional residual capacity remains an important goal in patients with large intracardiac shunts or single ventricle physiology, unnecessary use of supplemental oxygen and hyperventilation should be avoided as further reduction of PVR may be associated with increased pulmonary blood flow at the expense of systemic output.

14.3.6 Left Ventricular Preload/Pulmonary Venous Return

Respiration may alter LV preload as a result of changes in RV output, pulmonary vascular capacitance, compression of the cardiac fossa, and ventricular interdependence (Fig. 14.12). There is evidence to suggest that all of these mechanisms may contribute to decreasing LV preload under different baseline conditions. Because the RV and LV are in series, at steady state, left ventricular preload is ultimately dependent on the output of the RV. Therefore, any of the respiratory conditions discussed in the previous sections that decrease RV output will subsequently decrease LV preload and cardiac output.

LV preload may be altered by changes in pulmonary vascular capacitance. During spontaneous inspiration, subatmospheric intrathoracic pressures increase the capacitance of the intrathoracic vascular bed and result in a transient decrease in LV filling. The effect of PPV on pulmonary blood volume is dependent upon the intravascular volume status of the patient and is similar to the effect of respiration on the abdominal vascular compartment discussed previously (Fig. 14.10). When pulmonary artery and left atrial pressures exceed alveolar pressures (hypervolemic zone III conditions), then lung inflation with PPV leads to a transient increase in pulmonary venous return, a phenomenon known as thoracic pump augmentation. When alveolar pressures are greater than left atrial pressures during lung inflation (hypovolemic zone II

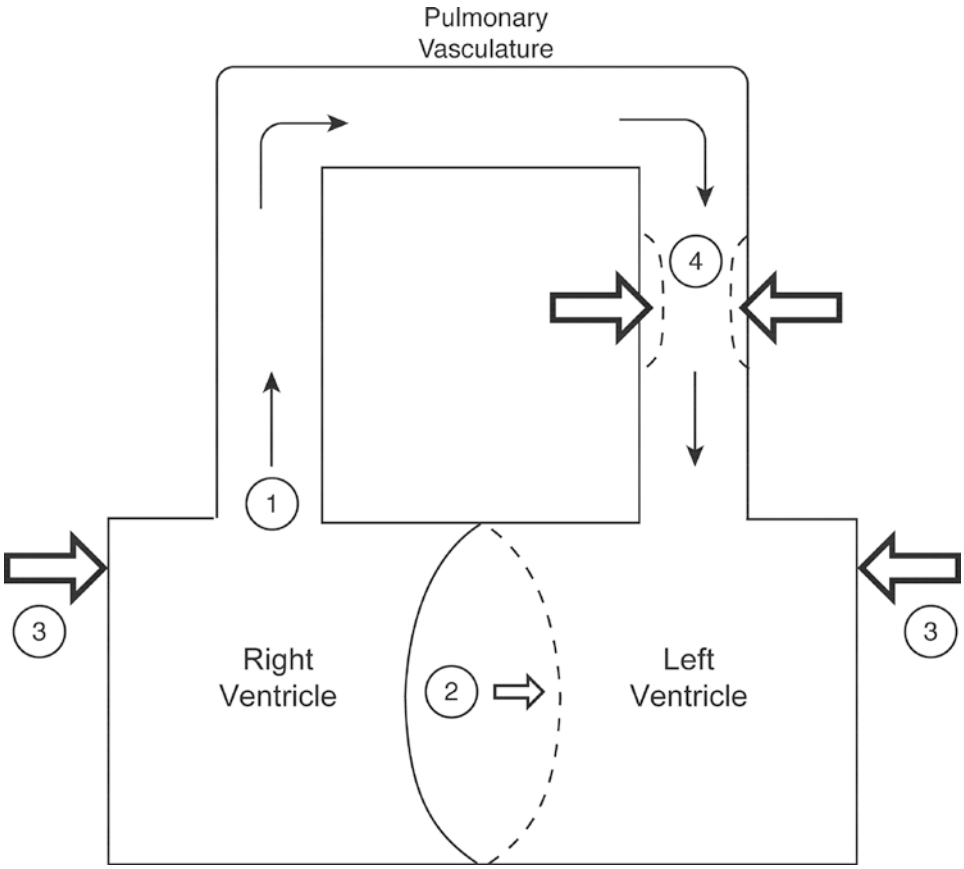


Fig. 14.12 Mechanisms by which left ventricle filling (preload) may decrease during respiration
1. Decrease in right ventricle (RV) output
2. Leftward deviation of the interventricular septum due to increased RV volumes (as a result of increased systemic venous return, increased RV afterload, and/or decreased RV contractility)
3. Compression of the cardiac fossa secondary to increased lung volumes
4. Decreased pulmonary venous return in hypovolemic states (zone 2 vascular compartment conditions) when transpulmonary pressures increase. In zone 3 conditions (hypervolemia) pulmonary venous return may increase as transpulmonary pressures are increased (Refer to Fig. 14.3)

An increase in venous return or RV afterload during respiration may transiently displace the interventricular septum into the LV, decreasing LV compliance and preload.

conditions), pulmonary venous return decreases. The importance of having adequate intravascular volume for LV preload is supported in both animal and human studies utilizing PPV during LV failure. Clinically, LV output during PPV is improved in patients with LV dysfunction associated with an increase in pulmonary blood volume (zone III conditions). Conversely, the use of PPV when LV filling pressures are normal or low can result in a decrease in cardiac output.

A salient feature of cardiopulmonary interactions is that the right and left ventricles share a septal wall and a space within the semirigid pericardium. Therefore, the combined volumes of the cardiac chambers cannot exceed the total volume of the pericardial space, a concept referred to as ventricular interdependence. When PPV results in increased RV afterload, RV diastolic volume increases and LV filling is reduced as a leftward shift of the interventricular septum occurs. An increase in venous return associated with subatmospheric intrathoracic pressure during spontaneous inspiration may also result in leftward deviation of the interventricular septum resulting in decreased LV compliance and diastolic volume. Clinically relevant situations in which this may occur include asthma and upper airway obstruction, where the combination of high lung volumes (increasing PVR and RV afterload) and increased venous return due to marked fall in intrathoracic pressure combines to decrease LV compliance, thus contributing to the pulsus paradoxus observed in severe asthma exacerbations. Reduced LV compliance is further enhanced by the compression of the cardiac fossa by the hyperinflated lungs and cardiac compression by the parietal pericardium, which is attached to the diaphragm and is pulled tight as the diaphragm is flattened. The use of PEEP greater than 15 cm H_2O in patients with acute respiratory distress syndrome has been asso-

ciated with a leftward shift of the interventricular septum due to an increase in RV afterload. In addition, similar to the effects from the hyperinflated lungs in an asthmatic patient, the use of PEEP can compress and limit the total volume of the cardiac fossa, resulting in smaller LV end-diastolic volumes and higher filling pressures. However, both of these effects of positive pressure are dependent on lung compliance; less compliant lungs limit transmission of pressure to the cardiovascular structures.

14.3.7 Left Ventricular Afterload

The influence of respiration on LV afterload occurs through changes in intrathoracic pressure acting on the external wall of the LV. The changes in intrapericardial pressures during respiration alter the transmural wall pressure of the LV, thus contributing to alterations in LV afterload. If the downstream aortic pressure and ventricular wall dimensions remain constant, the changes in external cardiac pressure during respiration may become the predominant factor in altering LV afterload. As described in more detail below, LV afterload is increased by negative pressure ventilation and decreased by positive pressure ventilation.

14.3.8 Negative Pressure Ventilation

Spontaneous respiration with airway obstruction increases LV afterload during inspiration by increasing transmural ventricular wall pressure.

The generation of negative pleural pressures during spontaneous breathing increases left ventricular afterload, which may decrease LV stroke volume and cardiac output (◘ Fig. 14.13a). From a mechanical standpoint, negative pleural pressures oppose the inward displacement of the ventricular wall during systole by generating a greater pressure gradient for the left ventricle to overcome. The spontaneously breathing asthmatic patient provides an example of how pleural pressure affects LV afterload. If normal left ventricular systolic pressure is 90 mm Hg and pleural pressure is 0 mm Hg, then the gradient that the LV must overcome to eject is 90 mm Hg. The asthmatic patient may generate significant negative (subatmospheric) pleural pressure during inspiration, which the LV must overcome in addition to the systolic pressure, that is, the asthmatic generating −20 mm Hg pleural pressure creates a pressure gradient that must be overcome by the contracting LV of 110 mm Hg, and hence, afterload is increased. The decrease in LV stroke volume with negative intrathoracic pressure is independent of changes in LV preload, lung volume, RV output, and RV volume, providing evidence that increased LV afterload is a significant contributor to decreased LV output during spontaneous breathing in conditions such as severe asthma. Cardiac output is usually maintained in the person with normal cardiac function, even with extremely negative intrathoracic pressures generated with airway obstruction. However, hypovolemia coupled with extreme negative intrathoracic pressure may result in a significant decrease in LV output, a common scenario in severe asthma. Similarly, while the normally functioning LV may be able to compensate for an increase in afterload during spontaneous breathing, the inability of the failing LV to overcome this increase in afterload may become clinically relevant. Pulmonary edema described with extreme negative pleural pressures in upper airway obstruction from laryngospasm, croup, and epiglottitis is explained by increased pulmonary blood volume as a result of increased LV afterload combined with increased venous return, which contributes in turn to higher capillary hydrostatic pressure, transcapillary fluid movement, and pulmonary edema. As noted previously, an increase in LV afterload contributes to the development of pulsus paradoxus during asthma and airway obstruction.

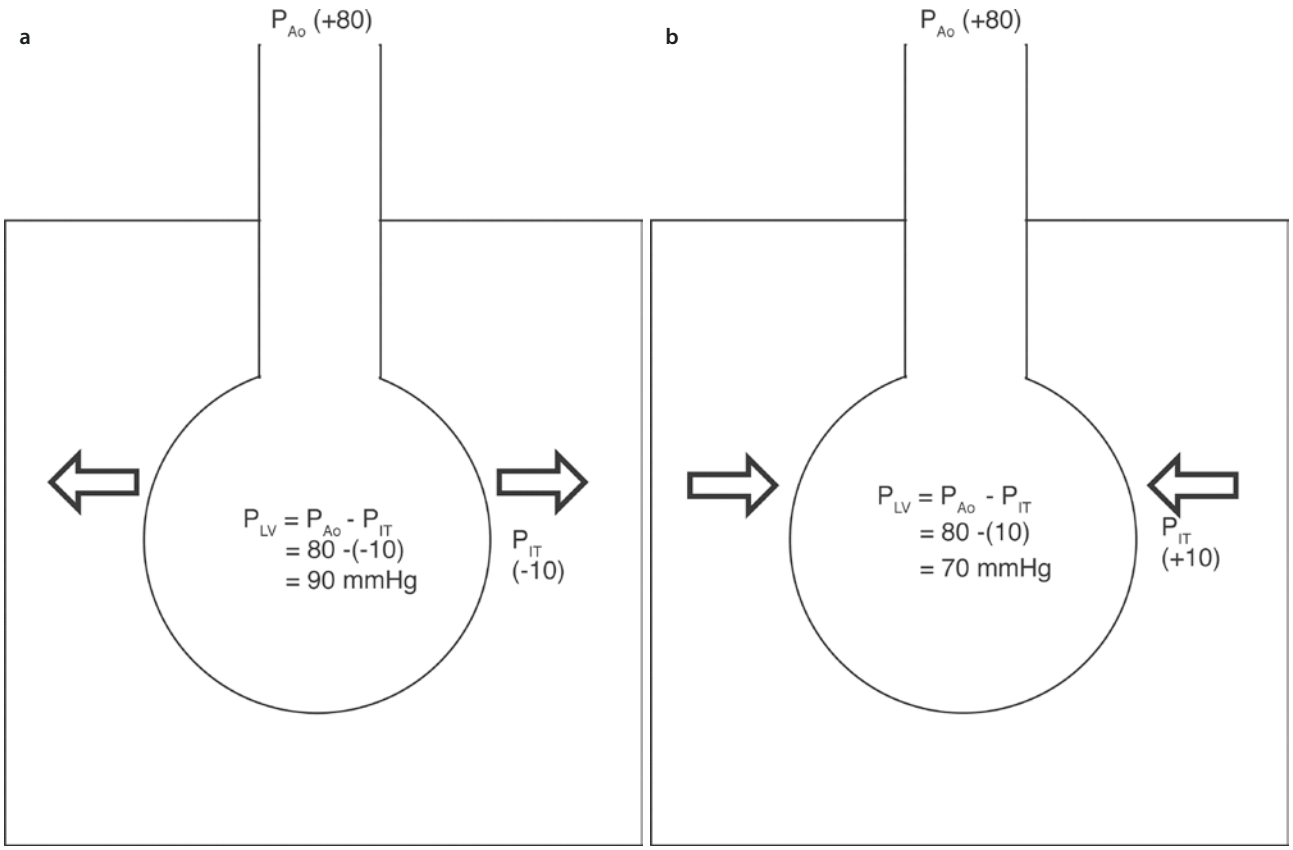


Fig. 14.13 **a** Left ventricular (LV) afterload during spontaneous respiration. LV afterload is proportional to the transmural LV wall pressure (difference between the arterial pressure (P_{AO}) acting on the internal ventricular wall and the intrathoracic pressure (P_{IT}) acting on the external surface of the ventricular wall) during systole. The total pressure or afterload the LV must overcome (P_{LV}) is the difference between P_{AO} and P_{IT}. **b** LV afterload during positive pressure ventilation. The increase in the surrounding intrathoracic pressures create an inward force exerted against the LV wall that reduces transmural left ventricular wall pressure, thus reducing LV afterload

14.3.9 Positive Pressure Ventilation

PPV has the opposite effect on LV systolic function by lowering the transmural wall pressure and decreasing LV afterload, resulting in improved LV function and cardiac output, assuming the patient has an adequate intravascular volume (Fig. 14.13b). As described previously during the inspiratory phase of a positive pressure breath, LV preload is increased secondary to augmented emptying of the pulmonary veins into the left atrium. The effect of improved LV systolic function during inspiration is most pronounced in patients with LV dysfunction. PPV also improves the economics of oxygen delivery and consumption in patients with decreased cardiac output. In the presence of congestive heart failure with its attendant decreased lung compliance and increased work of breathing, PPV reduces work of breathing and the demands on the heart to deliver oxygen to meet the metabolic needs of the respiratory muscles. Additionally, the use of CPAP in patients with asthma has been shown to decrease the work of breathing, heart rate, and LV afterload.

PPV decreases LV afterload by decreasing transmural ventricular wall pressure.

The importance of PPV effects in patients with LV dysfunction has been demonstrated in several clinical studies. Continuous positive airway pressure and PPV have been shown to increase stroke volume in adult patients with LV dysfunction and reduce mitral regurgitation in adult patients with heart failure and LV systolic dysfunction. The failure to pass spontaneous breathing trials and wean from mechanical ventilation is associated with significant LV dys-

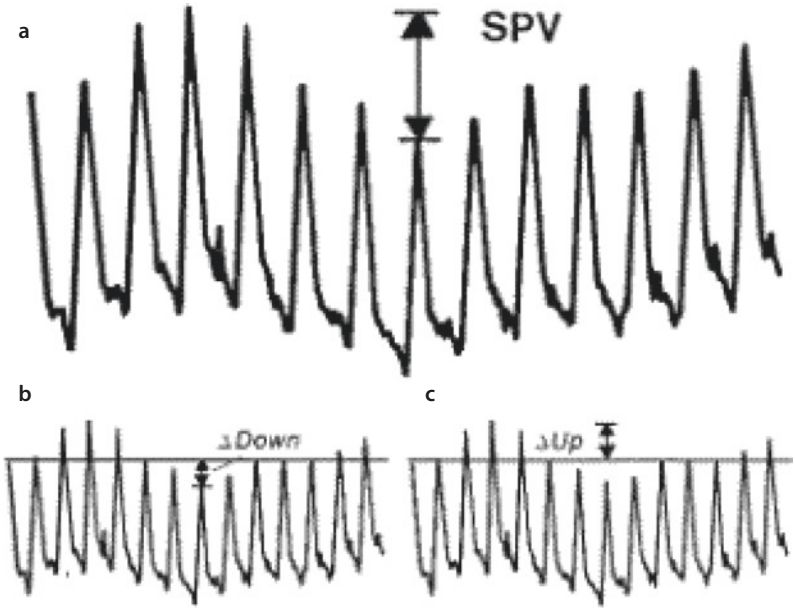


Fig. 14.14 Arterial blood pressure tracing demonstrating systolic pressure variation (*SPV*) during positive pressure ventilation. *Δ down* is the decrease in systolic pressure during early expiration. *Δ up* is the increase in systolic pressure during inspiration. The reference line is the systolic pressure during a short period of apnea at resting lung volume and is the baseline pressure from which Δ up and Δ down are calculated. (From Preisman et al. (1997))

function, manifested by the inability to increase cardiac output and meet the oxygen demands of respiratory muscles. For these reasons, the use of noninvasive PPV is a clinically relevant therapy to consider in any child with LV failure and respiratory distress.

Understanding the complex cardiopulmonary dynamics during positive pressure ventilation has led to the appreciation of systolic pressure variation. This term refers to the arterial pressure waveform changes that occur during positive pressure mechanical ventilation. The hemodynamic principles are similar to those in pulsus paradoxus, but instead of a fall in pressure during spontaneous negative pressure breathing, there is a transient rise in systolic pressure during the inspiratory phase of positive pressure breathing. This has led some to refer to this phenomenon as "*reverse pulsus paradoxus*"; however, *systolic pressure variation* (SPV) is the more correct term (Fig. 14.14).

A single positive pressure breath normally affects the arterial pressure in a biphasic manner. The initial response of a positive pressure breath is to "squeeze" pulmonary vascular blood into the LA (recall the opposite "pooling" of blood occurs with spontaneous negative pressure inspiration), augmenting LV preload leading to a rise in systolic pressure. In addition, positive intrathoracic pressure reduces the afterload on the LV further augmenting this early rise in arterial pressure. This is referred to as the Δ up component of SPV. Following this Δ up during early inspiration, a fall in systolic pressure occurs secondary to decreased systemic venous return and increased RV afterload during the positive pressure breath, which continues into the early expiratory phase. The transient reduction in RV preload and stroke volume impairs LV preload resulting in a smaller LV stroke volume and a brief reduction in arterial pressure that occurs later in the expiratory phase of the positive pressure breath (Δ down). Many studies have showed that SPV in mechanically ventilated patients can be quantified by a variety of methods and can be used to assess intravascular volume and assess fluid responsiveness (see ► Chaps. 16 and 34).

Clinically, an increase in SPV (>10 mm Hg) has been seen early in the setting of hypovolemia. This is due to an exaggerated Δ down component. Several studies observed an increase in the SPV occurring prior to a fall in arterial pressure and may be as predictive of hypovolemia as a low PAWP (<10 mm Hg). An increase in the SPV due to a greater fall in the Δ down component can also occur due to high airway pressures alone secondary to decreased venous return.

An increased SPV can also be seen when the Δ up component is increased rather than an exaggerated fall in the Δ down component. During a positive pressure breath, the Δ up component reflects a transient augmentation in the left ventricular stroke volume by increased LV preload and decreased LV afterload. This effect is increased in the setting of LV dysfunction. Therefore, a patient in CHF may have an increased SPV due to improved myocardial performance (augmented Δ up component) as a result of increased preload and decreased afterload while on positive pressure ventilation.

14.3.10 Effect of PPV on Contractility

The negative effects of PPV on myocardial contractility has been attributed to one of two mechanisms: (1) alterations in coronary artery perfusion leading to inadequate oxygen delivery to the myocardium and (2) the presence of myocardial depressant factors produced during PPV.

Myocardial contractility may be compromised by compression of coronary arteries during PPV.

In addition to decreased RV preload and increased afterload, the reduction in RV output at levels of PEEP around 20 cm H_2O may be due to a decrease in RV contractility. The effect of PEEP on RV function is more significant when RV function is depressed at baseline or when coronary artery blood flow is compromised prior to the use of PPV. The use of PEEP in adults after cardiopulmonary bypass is associated with decreased RV function, but only in a subset of patients with already established right coronary artery stenosis, a condition uncommon in children. When such predisposing conditions are present, addressing adequate right ventricular coronary perfusion becomes a priority. Interventions aimed at increasing coronary blood flow, such as increasing diastolic blood pressure or reducing PEEP and mean airway pressure, should be considered. A limited number of animal studies support compression of coronary arteries as a potential mechanism for decreased cardiac contractility during PPV. In isolated animal hearts, an increase in pressure on the external surface of the heart decreased coronary artery blood flow and produced myocardial ischemia, providing indirect evidence that PPV may contribute to a decrease in myocardial contractility by compromising coronary blood flow.

Compared to the mechanical effects on cardiac function during PPV, the release of circulating factors that depress myocardial function is probably not of major importance in cardiopulmonary interactions. Although some investigators have found evidence of decreased LV contractility during PPV, most studies have not demonstrated a detrimental effect on LV contractility in animals or humans during the use of PPV or PEEP. Animal studies provide conflicting results on the role neural reflexes and circulating chemical mediators (such as prostaglandins or cytokines) play in decreasing myocardial function during mechanical ventilation. Separating the effect of mechanical forces on the heart during PPV from the effect that circulating mediators may have on myocardial contractility is difficult, especially in the intact cardiopulmonary system. In summary, the primary effects of PPV on cardiac function appear to be the mechanical influences on preload and afterload, while the effect of PPV on myocardial contractility appears to play a lesser role.

14.3.11 Cardiac Effects on Respiratory Function

The ability to maintain an adequate cardiac output to meet the metabolic demands of respiratory muscles is the major effect of cardiac function on respiratory function.

One of the most important effects the heart has on pulmonary function is the adequate delivery of oxygen to meet the metabolic demands of respiratory muscles. When cardiac output is insufficient to meet the respiratory muscle oxygen requirement, respiratory failure occurs. Although patients with normal cardiovascular function can meet the increase in metabolic requirements of the respiratory muscles during illness, the patient with decreased cardiac function may be unable to meet respiratory muscle oxygen demand and is at high risk for respiratory muscle failure. This has been demonstrated in an experimental model of obstructive shock due to tamponade. Canine subjects that were artificially ventilated survived the period of poor cardiac output while all of the canines that were allowed to spontaneously breathe during cardiogenic shock died secondary to respiratory failure. No changes occurred in the mechanical properties of the respiratory system, and death was due to impairment of respiratory muscle contraction. These findings emphasize the importance of interventions that improve cardiac output, decrease the work of breathing, or both during cardiopulmonary dysfunction that reestablishes the balance between oxygen delivery and consumption. Therefore, PPV can be beneficial in patients with poor LV function and respiratory failure by reducing the work of breathing, decreasing oxygen consumption of the respiratory muscles, and reducing LV afterload.

Alterations in cardiac output can affect gas exchange in the lung by changing ventilation and perfusion matching.

Another important cardiac effect on lung function relates to the matching of ventilation and perfusion in the lung. When cardiac output is decreased, there is an increase in the area of lung that is ventilated but not well perfused (West Zone 1; see ◘ Fig. 14.15). The application of PPV in this circumstance may increase dead space ventilation by increasing alveolar pressures and decreasing venous return. An extreme example of this physiology is a patient in cardiopulmonary arrest with adequate ventilation but poor pulmonary blood flow. In this example and others with poor cardiac output, increasing cardiac output improves matching of ventilation with perfusion and gas exchange (Zones 2 and 3).

The existence of an intrapulmonary shunt significantly affects the gas exchange function, which can also be affected by changes in cardiac output. Patients with pulmonary shunts with low cardiac output, and therefore low venous blood oxygen saturation, also have decreased oxygen saturation of blood returning to the left atrium. Systemic arterial oxygen saturation can be improved by increasing cardiac output and thus systemic venous oxygen saturation (see ◘ Fig. 14.16).

Acute lung injury is often inhomogeneous so that alveoli have varying levels of compliance; therefore, PPV with high levels of PEEP may worsen gas exchange by overdistending compliant alveoli and compressing their associated alveolar capillaries. Blood is then shunted to capillaries associated with noncompliant alveoli that are not participating in gas exchange. When this occurs in conjunction with a decrease in cardiac output, the effect is to increase dead space ventilation and physiologic shunting, resulting in ineffective gas exchange. High airway pressures or PEEP may also contribute to poor arterial oxygenation if this results in over-distension of the lung volume by increasing pulmonary vascular resistance and increasing right to left shunts through an existing patent foramen ovale, atrial septal defect, or ventricular septal defect. Lung volume, not pressure, is the most important contributor of pulmonary vascular resistance as noted in the previous section on RV afterload.

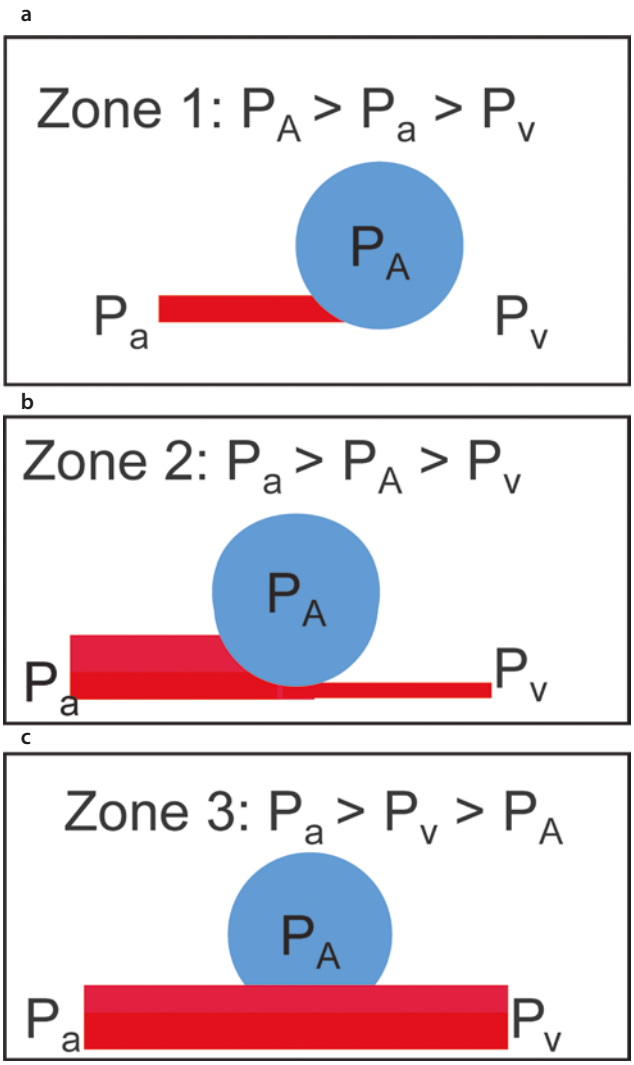


Fig. 14.15 Decreased right ventricle (RV) output may increase *Zone 1* (area of dead space ventilation) in the lung **a** as fewer alveoli are associated with capillary blood flow associated with increased intra-alveolar pressure. Increasing RV output increases the *Zones 2 and 3* conditions of the lung **b**, **c**, increasing the number of alveoli participating in gas exchange. *PA* alveolar pressure, *Pa* pulmonary artery pressure, *Pv* pulmonary vein pressure

In children with congenital heart disease, alterations in pulmonary blood flow and pulmonary artery pressure have been shown to effect lung mechanics. Increases in pulmonary blood flow associated with increased pulmonary artery pressures result in decreased lung compliance and increased airway resistance. The changes in lung mechanics that occur with pulmonary artery hypertension may have several etiologies including displaced lung volume by an enlarged heart and/or increased pulmonary blood volume, increased interstitial lung fluid, mechanical compression of the smaller airways or alveoli, and bronchoconstriction. There is some evidence that airway muscle hypertrophy and bronchoconstriction play a significant role in changing lung mechanics during pulmonary artery hypertension. The existence of smooth muscle hypertrophy in both pulmonary vasculature and respiratory airways may be explained by the action of local mediators that stimulate smooth muscle hypertrophy in both airways and vascular beds.

Pulmonary hypertension and increased pulmonary blood flow result in increased transcapillary fluid movement into interstitial tissues, which contribute to a decrease in pulmonary compliance and increase in airway resistance.

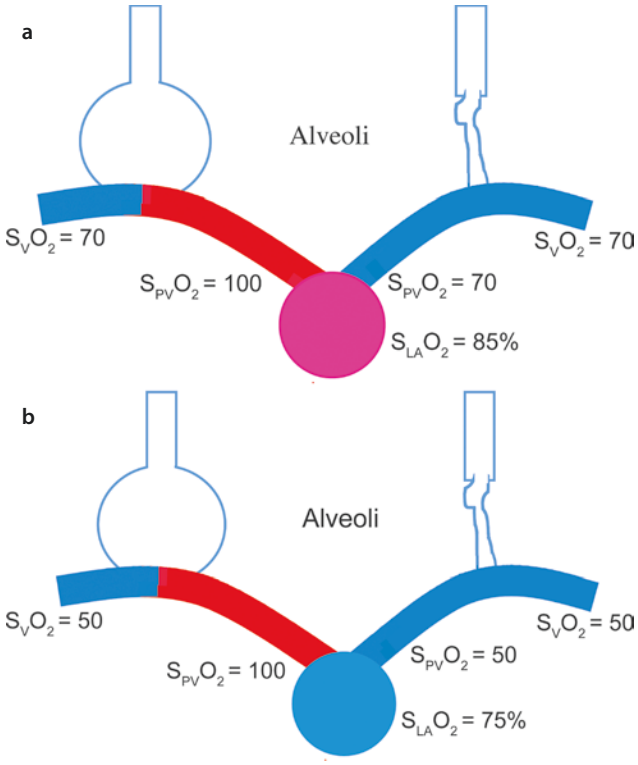


Fig. 14.16 **a** The effect of a 50% pulmonary shunt on left atrial oxyhemoglobin saturation ($S_{LA}O_2$) when cardiac output is normal. **b** With the same shunt, a decrease in venous oxygen saturation (S_VO_2) associated with poor cardiac output results in lower $S_{LA}O_2$. Increasing cardiac output **a** improves arterial hemoglobin oxygen saturations in patients with pulmonary shunts. $S_{PV}O_2$ pulmonary venous oxyhemoglobin saturation

14.3.12 Cardiopulmonary Interactions in Patients with Fontan Physiology

A clear understanding of cardiopulmonary interactions is crucial to managing children with Fontan physiology. Following the Fontan procedure, pulmonary blood flow is completely passive and dependent on complex cardiopulmonary interactions that affect the pressure gradient between the systemic venous system and the systemic ventricle's atrium. Sufficient preload, minimal PVR (i.e., afterload), low systemic ventricular end-diastolic pressure, and adequate systemic ventricular function are all key determinants of passive pulmonary blood flow and hence cardiac output. However, adequate pulmonary blood flow is mainly dependent on low PVR, which is highly sensitive to changes in intrathoracic pressure, lung volumes, and ventilation. Although PPV decreases afterload and increases cardiac output in a failing LV in an otherwise normally structured heart, a substantial decrease of systemic ventricular afterload without preload reserve in the patient with Fontan physiology will not increase cardiac output. Instead, the use of any PPV may decrease cardiac output in the patient with Fontan physiology by increasing lung volumes and PVR and decreasing systemic venous return secondary to increased intrathoracic pressure. Clinical experience in patients after Fontan procedure shows that even in the absence of the active RV pump, cardiac output can be maintained by optimizing lung volume, minimizing PVR, and avoiding positive intrathoracic

pressure. Therefore, patients with Fontan physiology often benefit from early weaning from PPV, extubation, and spontaneous breathing.

However, when weaning from PPV cannot be achieved secondary to acute lung injury or hemidiaphragmatic paralysis, patients with Fontan physiology benefit from ventilatory strategies that optimize lung volumes around FRC and by minimizing peak, positive end-expiratory, and mean airway pressures. Use of other unconventional ventilation modalities may also be considered when conventional mechanical ventilation fails to improve gas exchange and maintain cardiac output in patients with severe lung disease and Fontan physiology. For example, high-frequency jet ventilation may be effective in reducing mean airway pressure and increasing cardiac output. Similarly, the use of high-frequency oscillation ventilation (HFOV) in patients after Fontan operation had no significant effect on cardiac output or PVR. This latter finding may be explained by the importance of optimizing lung volumes to reduce PVR and the difference in airway and pleural pressures in the poorly compliant lung. Negative pressure ventilation (NPV) has also been used to manage the low cardiac output state in Fontan patients with significant lung injury. Although augmentation of venous return by NPV is ultimately limited by collapse of the extrathoracic blood vessels, the high baseline intravascular volume status and venous pressures in Fontan patients makes this phenomenon less likely when NPV is utilized in these patients. However, the use of alternative modes of mechanical ventilation has not gained widespread use in the management of Fontan patients due to the recognized advantages of early extubation to spontaneous breathing.

In summary, after Fontan operation, consideration should be given toward optimizing lung volumes, minimizing airway pressure, addressing pleural space pathology, maintaining adequate intravascular volume and preload, and proceeding toward spontaneous negative pressure breathing as soon as it is feasible.

Fontan physiology is analogous to a waterfall where the systemic and AV valves intermittently form locks regulating flow, allowing blood to flow downstream to lower pressure environments until the single ventricle pumps it back upstream.

14.4 Summary of Cardiopulmonary Interactions

Factors important in cardiopulmonary interactions include understanding the changes in intrathoracic pressure and lung volume during spontaneous versus positive pressure respiration, the effects of intravascular volume status, and the baseline function of the heart and lungs. In many situations, the baseline condition of the patient, including the intravascular volume status and myocardial function, will determine the ultimate clinical effect, if any, that the cardiac and respiratory systems may have on each other. Anticipation of heart-lung interactions during support of the critically ill child promotes early recognition of alterations in cardiopulmonary function and prevents deleterious effects of therapy (◘ Fig. 14.17).

2. Leftward deviation of the interventricular septum due to increased RV volumes (as a result of increased systemic venous return, increased RV afterload, and/or decreased RV contractility)

3. Compression of the cardiac fossa secondary to increased lung volumes

4. Decreased pulmonary venous return in hypovolemic states (Zone 2 vascular compartment conditions) when transpulmonary pressures increase. In Zone 3 conditions (hypervolemia), pulmonary venous return may increase as transpulmonary pressures are increased (refer to ◘ Fig. 14.10)

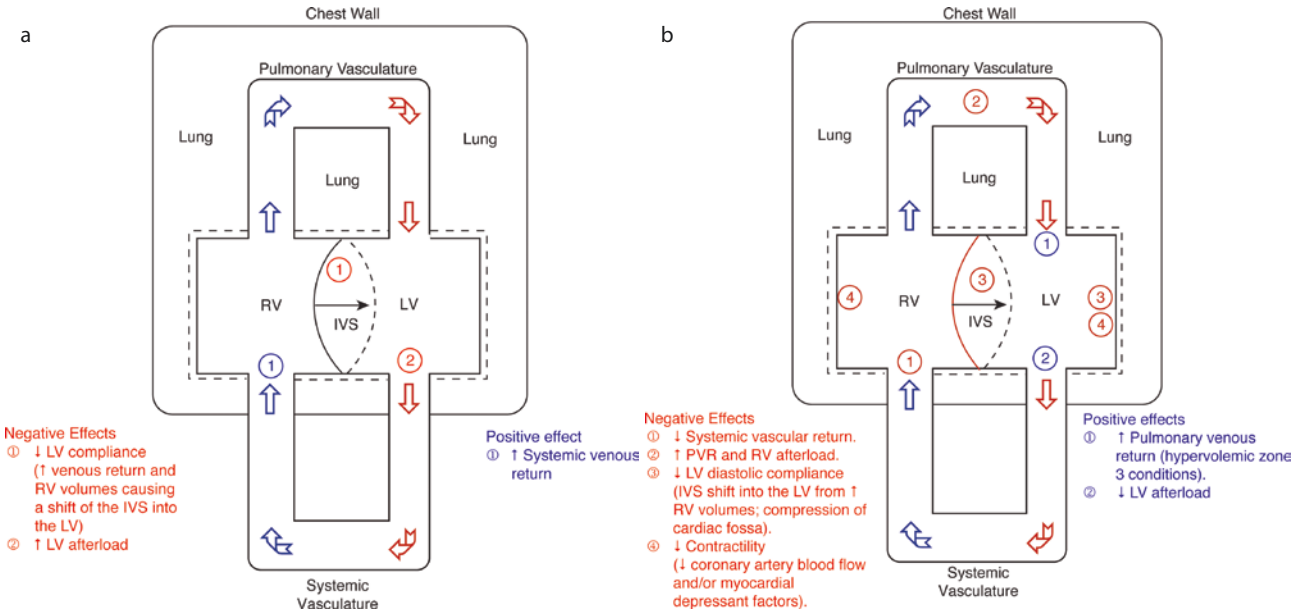


Fig. 14.17 **a** Summary of the primary effects of spontaneous respiration on cardiac function. **b** Summary of the primary effects of positive pressure ventilation on cardiac function. *RV* right ventricle, *LV* left ventricle, *IVS* interventricular septum

Review Questions

1. A 6-month-old infant undergoes a VSD repair due to heart failure symptoms and failed medical management, including poor growth velocity. The postoperative course is complicated by third-degree heart block with a ventricular escape rhythm. Which finding is most likely to be noted on a CVP tracing of this patient?
   A. Giant V waves
   B. Change in the slope of the y descent
   C. V wave with an increased amplitude compared to the A wave
   D. Cannon A waves
   E. Loss of the C pressure wave

2. During what phase of the cardiac cycle is aortic pressure the highest?
   A. Ventricular filling
   B. Ventricular ejection
   C. Atrial systole
   D. Isovolemic relaxation
   E. Isovolemic contraction

3. While evaluating an 11-month-old, 10 kg infant with tachycardia (180 beats per minute) and poor perfusion, the critical care physician notes that the heart rate decreases momentarily to 170 beats per minute, and the pulses became stronger after compressing the liver of the infant. Which of the following physiological changes most likely explains the response?
   A. The compression on the liver produced a sudden increase in the systemic vascular resistance, and the increased afterload resulted in the stronger pulses and decreased heart rate.
   B. The compression on the liver produced a sudden vagal response clinically manifested by the decreased heart rate.
   C. The compression on the liver produced a temporary increase in contractility with a resultant increase in cardiac output (stroke volume) and a slowing of the heart rate.

D. The compression on the liver reduced venous return to the heart, thereby decreasing preload resulting in clinical deterioration manifested by the decreased heart rate.
E. The compression on the liver transiently increased preload with a resultant increase in cardiac output (stroke volume) and a reflexive slowing of the heart rate.

4. A 2-month-old infant presents with renal failure secondary to an obstructive uropathy. The infant is tachypneic and noted to have a metabolic acidosis with a blood pH of 7.20. Sodium bicarbonate (1 mEq/kg) is administered intravenously in an attempt to improve the blood pH. Shortly thereafter, the infant's perfusion is clinically noted to decline. Which of the following is the best potential explanation for the change in hemodynamics?
   A. Despite bicarbonate therapy, the blood pH remained sufficiently low to negatively affect the myocardium.
   B. The increase in the blood pH further reduced the low plasma-ionized calcium concentration, negatively affecting myocardial contractility.
   C. The increase in the blood pH led to direct systemic vasodilatation resulting in hemodynamic compromise.
   D. The rapid rise in sodium concentration resulted in a negative inotropic effect on the heart.
   E. The respiratory rate increased further after the bicarbonate therapy resulting in further energy expenditure and cardiovascular compromise.

5. A previously healthy 10-year-old child develops ARDS after sustaining abdominal and lower extremity trauma in a motor vehicle collision. She received crystalloid fluid resuscitation and multiple blood product transfusions to achieve hemodynamic stability. She requires a positive end-expiratory pressure (PEEP) of 15 cm H_2O to maintain acceptable arterial oxygenation but develops poor cardiac output with this ventilator strategy. Which of the following is the most likely primary cause of her decreased cardiac output?
   A. A decrease in left ventricular contractility due to myocardial depressant factors
   B. A decrease in left ventricular filling due to interventricular septal shift into the left ventricle
   C. A decrease in systemic venous return secondary to increased mean airway pressure
   D. An increase in left ventricular afterload due to increased transmural wall pressure
   E. An increase in right ventricular afterload secondary to lung overdistension

6. Which of the following is a contributing factor in the clinical presentation of pulsus paradoxus?
   A. A decrease in left ventricular afterload
   B. A decrease in pulmonary vascular resistance
   C. An increase in myocardial contractility
   D. An increase in right ventricular volume
   E. A rightward shift of the interventricular septum

7. A 3-year-old male with a known cardiomyopathy and decreased left ventricular function is admitted to the pediatric intensive care unit with a presumed viral laryngotracheobronchitis. In addition to reducing the work of breathing, tracheal intubation and the use of positive pressure ventilation will benefit cardiac function in this child in which of the following ways?
   A. A decrease in left ventricular afterload
   B. A decrease in right ventricular afterload
   C. A decrease in systemic venous return
   D. An increase in cardiac contractility
   E. An increase in systemic venous return

8. A 12-year-old male with a severe asthmatic exacerbation has worsening respiratory distress that is now accompanied by poor perfusion, worsening tachycardia (190 beats per minute), and hypotension (83/56 mm Hg). The physiologic explanations for the hypotension include relative hypovolemia secondary to increased insensible water losses and decreased intake, hypoxemia-induced myocardial dysfunction, and
   A. Decreased right ventricular afterload
   B. Decreased systemic vascular resistance
   C. Increased left ventricular afterload
   D. Increased partial pressure of carbon dioxide
   E. Untoward effect of steroid therapy

9. A 12-year-old male with a severe asthmatic exacerbation has now developed compromised perfusion with significant tachycardia (185 beats per minute) and hypotension (82/42 mm Hg). An appropriate initial hemodynamic intervention in this child would be to:
   A. Administer a crystalloid fluid bolus (10 mL/kg) to augment preload
   B. Initiate a low-dose epinephrine infusion (0.05 mcg/kg/min) to augment contractility
   C. Initiate an infusion of milrinone (0.5 mcg/kg/min) to augment contractility and foster ventricular relaxation
   D. Initiate an infusion of sodium nitroprusside (1 mcg/kg/min) to decrease systemic afterload
   E. Initiate inhaled nitric oxide (20 ppm) to decrease pulmonary vascular resistance

10. Which of the following statements regarding cardiovascular-pulmonary interactions is *false*?
   A. An increase in systemic venous return or in right ventricular afterload during respiration may displace the interventricular septum into the left ventricle and decrease left ventricular compliance and preload.
   B. Extremes in lung volumes (both low and high) can result in elevations in pulmonary vascular resistance.
   C. Adequate intravascular volume is important for both RV and LV output when initiating positive pressure ventilation.
   D. Negative intrathoracic pressure generated during spontaneous breathing increases the pressure gradient from the systemic veins to the right atrium.
   E. Negative intrathoracic pressure generated during spontaneous breathing has no effect on extrathoracic large veins.

Answers

1. D
2. B
3. E
4. B
5. C
6. D
7. A
8. C
9. A
10. E

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Regional Circulations

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Contents

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Learning Objectives

- Describe the relative proportions of blood flow and oxygen consumption in the pulmonary, cardiac, renal, splanchnic, and cutaneous circulations.
- Describe the mechanisms that change regional blood flow in response to stress and pathological conditions.
- Summarize the role of the microcirculation in determining regional blood flow.
- Describe the unique characteristics of the coronary, cerebral, pulmonary, splanchnic, and renal vasculature.
- Describe the importance of local regulation of blood flow and mechanisms for achieving local control, including autoregulation of flow to major organ systems.
- Describe differences in oxygen extraction ratio in different organs, including the high oxygen extraction in the heart and the brain and relatively low extraction in the kidney.
- Describe the mechanisms of hypoxic pulmonary vasoconstriction.
- Review causes of increased and decreased pulmonary vascular tone.
- Review the importance of control of cerebral vascular tone in specific conditions.
- Understand the mechanisms and effects of control of cutaneous vascular tone.

15.1 Regulation of Blood Flow and Oxygen Consumption at the Major Tissue Beds

The major role of the circulatory system is to supply all the tissue beds with oxygen and nutrients and remove the end products of metabolism. During critical illness or injury, the circulatory system must adjust flow to organs and tissues to assure adequate flow to vital organs (i.e., the heart and the brain). The uninterrupted flow of oxygen and nutrients is necessary to sustain viability and function of the many specialized tissues. Since energy is needed for any function in the human body and it can be provided only by nutrients and oxygen, it is only logical that through the billions of years of evolution, all the tissues developed regulatory mechanisms that couple their function and energy consumption with substrate delivery by the circulatory system.

The vascular system components each play a role in the distribution and control of blood flow. *Large arteries* are responsible for distribution of blood flow and contribute very little to vascular resistance and blood flow regulation under normal conditions. Large arteries have sympathetic innervation, but increased smooth muscle tone in these vessels does little to change resistance; instead, it makes the artery stiffer (i.e., less compliant).

Small arteries range from 0.2 to 1.0 mm in diameter and provide vascular resistance that helps determine blood flow distribution. The small arteries typically distribute blood within an organ.

Arterioles are 0.01–0.2 mm (10–200 μm) and provide pressure and flow regulation by altering their resistance. Both small arteries and arterioles are typically highly innervated by autonomic nerves (especially from the sympathetic nervous system (SNS)). Together, these are the resistance vessels. Note that increased vascular tone not only reduces flow to the area of distribution, but it also decreases capillary hydrostatic pressure, which favors interstitial fluid absorption. It is important to recognize that SNS distribution to the vas-

cular beds is not uniform. For example, autonomic innervation in the splanchnic, skin, and skeletal muscle vascular beds is more extensive, which can selectively redirect blood flow from those beds when flow to more critical vascular beds must be preserved.

Capillaries are 6–10 μm, venules are 10–200 μm, and veins are 0.2–5 mm (200–5000 μm). Venules and veins are often innervated and help regulate blood flow and distribution. In most vascular beds, postcapillary resistance only contributes ~15% to the overall vascular resistance, but this is higher (~30%) in the pulmonary circulation and may be higher in pathological conditions.

About 70–75% of blood volume is in the venous vasculature. Thus, the veins serve as a capacitance reserve system; increased SNS activity reduces venous compliance considerably, which helps increase venous return by reducing the size of the vascular tank. Increased venous tone also increases venous pressure in extrathoracic veins creating a pressure gradient with the right atrium favoring venous return. Of note, the parasympathetic nervous system does not directly innervate arteries or veins (with a few exceptions) but can modulate SNS activity.

All the different tissue beds can autoregulate the amount of blood flow they receive to meet their needs. Although many individual differences exist, there are major similarities. The *myogenic response* describes the mechanism by which vessels respond to an increase in transmural pressure or stretch by constricting, thereby restoring blood flow to baseline levels. This is mediated by opening of mechanosensitive cation channels, principally Na^+, which depolarizes the cell membrane, thus activating voltage-gated Ca^{2+} channels that increase intracellular calcium concentration, which leads to smooth muscle contraction. Conversely, a fall in transmural pressure reduces vascular tone.

Tissue hypoxia (i.e., low partial pressure of oxygen in the tissues) leads to vasodilation in the local tissue arteriolar structures, which increases the flow of oxygenated blood into the territory. That is true for all tissues except the pulmonary circulation where tissue hypoxia leads to pulmonary arterial vasoconstriction. The reason for that difference is discussed in detail in the pulmonary circulation section.

15

Tissue hypoxia is a potent regulator of regional blood flow.

Tissue hypoxia causes vasodilation in all vascular beds except in the pulmonary circulation.

Note that tissue *hypoxia* is not the same as *hypoxemia* (i.e., low *blood* partial pressure of oxygen). There are four major causes of tissue hypoxia: (1) ischemic hypoxia (i.e., inadequate blood flow); (2) anemic hypoxia where there is inadequate oxygen carrying capacity, such as seen with aplastic crisis in sickle cell disease; (3) hypoxemic hypoxia as seen in a patient with severe acute respiratory distress syndrome; and (4) histotoxic hypoxia, such as seen with carbon monoxide or cyanide poisoning, but also seen in some patients with sepsis who have an impaired ability to utilize oxygen. Not infrequently, tissue hypoxia results from a combination of more than one of these factors. Understanding the underlying cause(s) of tissue hypoxia helps direct therapy to reverse this condition.

There are four major causes of tissue hypoxia: (1) inadequate blood flow (ischemic hypoxia), (2) low oxygen carrying capacity (anemic hypoxia), (3) low arterial oxygen saturation (hypoxemic hypoxia), and (4) impaired ability to metabolize oxygen (histotoxic hypoxia). One or more of these factors may occur in a patient.

Metabolism produces byproducts (e.g., CO_2, adenosine, protons, and 2,3-diphosphoglycerate); accumulation of these byproducts influences the arteriolar tone leading to vasodilation and increased blood flow. High levels of tissue CO_2 significantly increase cerebral and striate muscle blood flow, and adenosine dilates maximally the coronary arteries.

The myogenic response is a major mechanism that autoregulates regional blood flow.

Besides direct activation of vascular smooth muscle cells (VSMC) by norepinephrine released from sympathetic nerves, important actions on vascular tone are mediated by hormonally acting epinephrine released from the adrenal

gland. Although norepinephrine is also released from the adrenal gland (~20% of total catecholamine released), the latter normally does not act as a circulating hormone on adrenergic receptors. The actions at adrenergic receptors are determined by whether they are innervated or hormonal receptors (see ▶ Chap. 20, "Vasoactive Agents"). Sympathetic nerves terminate at α_1- and $ß_1$-adrenoceptors, whereas the hormonal effects of epinephrine are mediated through action at α_2- and $ß_2$-adrenoceptors. Differential actions in organs are mediated in large part by the density of different adrenoceptor types and the extent of tissue innervation by sympathetic nerves in the tissue beds. For example, there is a high density of $ß_2$-adrenoceptors in skeletal muscle vascular beds; thus, when epinephrine is released from the adrenal gland, it selectively increases blood flow to the skeletal muscles to address the energy needs to either run or fight a predator. Under the same stress, activation of SNS nerves in the skin, renal, and splanchnic circulation reduces blood flow to those organs and constricts capacitance veins increasing venous return.

15.1.1 Local Hormonal/Nervous System Factors Affecting Vascular Tone

Although the dynamic balance between sympathetic and parasympathetic nervous system outputs plays an important role in regulating blood flow, it is important to recognize that these autonomic systems interact with a complex array of factors that also influences vascular tone, especially during a critical illness. These additional factors explain much of the variation in clinical action observed when exogenous vasoactive drugs are infused to adjust blood flow and pressure (see ▶ Chap. 20, "Vasoactive Agents").

A wide range of local or systemic mediators either stimulate vasoconstriction or vasodilation, as summarized in ◘ Table 15.1. Besides direct action on VSMC or endothelial receptors, some mediators modulate sympathetic nervous system activity. For example, angiotensin is not only a direct vasoconstrictor, but it also acts at presynaptic angiotensin receptors to increase norepinephrine release from sympathetic nerves.

Since most mediators work through receptor systems, it is also important to recognize that receptors are dynamic structures on the cell surface that are actively regulated in terms of their density, surface presentation, and activity. For example, tonic stimulation of a receptor by an agonist typically leads to downregulation of the receptor. Conversely, blocking the receptor (e.g., with a ß-adrenoceptor blocker) increases receptor density on the cell surface.

To add to the complexity of VSMC tone regulation, receptors activate various internal signaling systems, such as G-proteins that either stimulate or inhibit various enzyme systems in the cell, leading to an increase or decrease in secondary message systems, such as cGMP, cAMP, inositol triphosphate, and diacylglycerol. These messengers then act at various enzyme systems that ultimately regulate cytoplasmic calcium concentration. These enzyme systems are also regulated, most often by the addition or removal of phosphate.

Besides acting directly on VSMC, a number of mediators exert their action by stimulating or inhibiting endothelial nitric oxide (NO) production. Thus, injury to the endothelium, which may occur during sepsis, trauma, etc., may impair the ability of local endothelium to produce NO, leading to increased vascular tone, as well as predisposing to activation of the clotting system.

Table 15.1 Summary of the actions of mediators on vascular smooth muscle tone

Mediator	Reduce vascular tone	Increase vascular tone
Norepinephrine	N/A	Acts at α_1- and α_2-adrenoceptors
Epinephrine	Acts at $ß_2$-adrenoceptors	Acts at α_1- and α_2-adrenoceptors
Angiotensin II		VSMC receptor; also acts on presynaptic receptors to increase NE release from sympathetic nerves
Vasopressin	Oxytocin receptors in pulmonary vascular bed	V_1 VSMC receptor
Endothelin (ET-1)	Action at ET_B on endothelial cells stimulates local NO production	Through ET_A and ET_B receptors on VSMC
Histamine	VSMC and endothelial receptors in systemic vascular bed	VSMC receptor in pulmonary circulation, especially in pulmonary venules
ANP and BNP	VSMC receptors	
Bradykinin	VSMC receptors	
NO	Intracellular activation in VSMC of cGMP production	
PGE_1 and PGI_2	VSMC receptors and endothelial receptors (the latter increase NO)	
Thromboxane (TXA_2)		VSMC receptors
$PGF_{2\alpha}$ and PGE_2	VSMC in pulmonary circulation	
Adenosine	Acts on endothelial receptors to increase NO release	
EDHF	Released by endothelium and hyperpolarizes VSMC	
Tissue hypoxia	Hypoxia-inducible factor (HIF) production and unclear mechanisms to reduce VSMC tone in systemic circulation	Acts at oxygen-associated K^+ channel in pulmonary VSMC
Increased tissue CO_2	Reduces tone in VSMC in systemic circulation	Increases tone in VSMC in pulmonary circulation by unclear mechanism
K^+	Increased tissue K^+ activates K^+-dependent K^+ channels, which hyperpolarizes VSMC	

VSMC vascular smooth muscle cells, *ET_A and ET_B* are endothelin A and B receptors, *NO* nitric oxide, *ANP and BNP* atrial and B-type natriuretic peptide, *EDHF* endothelium-derived hyperpolarizing factor

In summary, it should be clear that simple explanations of changes in blood flow due to changes in SNS activity, for example, are unlikely to fully explain what happens during critical illness when the VSMC receives conflicting "messages" from various mediators. More details on the role of various mediators on blood flow in specific regional vascular beds are provided in the following sections.

Detailed review of all the mediators noted in Table 15.1 is beyond the scope of this chapter. The following section reviews several important mediators and mechanisms that control VSMC tone.

Endothelium-Derived Vasoactive Factors

- *Nitric oxide*: Nitric oxide (NO) diffuses from the endothelium and potently relaxes the overlying VSMC resulting in vasodilation. In some arterial territories, NO also produces vasodilation through the activation of potassium channels resulting in cell hyperpolarization. Nitric oxide is produced in endothelial cells by NO synthase from L-arginine, where it then diffuses into smooth muscle cells and activates soluble guanylate cyclase, which increases the intracellular concentration of cGMP. Increased cGMP, through several intermediate steps, relaxes VSMC tone. Several pieces of evidence suggest that endothelial NO synthase (NOS) activity plays an important role in arterial basal tone. Inhibitors of NOS decrease intracellular cGMP concentrations producing vasoconstriction. Injury to the endothelium also increases tone in the overlying vessel.

  The concentration of NOS is also controlled by up- or downregulation of its gene expression. Shear stress, cGMP, transforming growth factor β1, atherosclerosis, cirrhosis, and pregnancy upregulate the gene, while LDL cholesterol (oxidized), hypoxia, TNFα, and heart failure downregulate the gene.
- *Prostacyclin*: Prostacyclin is a product of arachidonic acid synthesized by the cyclooxygenase enzymes, COX1 and 2. Prostacyclin produced in endothelial cells causes significant vasodilation by acting at VSMC receptors to increase intracellular cAMP, activation of potassium channels, and possibly by increased NO production; it also is a potent inhibitor of platelet aggregation.
- *Endothelium-derived hyperpolarizing factor (EDHF)*: In addition to NO and prostacyclin, the endothelium relaxes smooth muscle by releasing EDHF, which is thought to be a soluble transferable factor that causes smooth muscle cell hyperpolarization inhibiting smooth muscle contraction. The impact of EDHF on vasodilation and arterial tone is inversely related to the size of the artery; thus, EDHF has a greater effect than NO in smaller arteries. Inhibition of NO and prostacyclin does not eliminate the action of EDHF, indicating that it is some yet to be determined factor. Hyperpolarization of the cell membrane by EDHF is mediated by activation of ATP-sensitive and calcium-dependent potassium channels. Some data suggest that it may be different factors in different tissues, with data supporting hydrogen peroxide, sulfur dioxide, and potassium ions as mediators.
- *Endothelin*: Endothelin is one of the few vasoconstricting endothelial-derived mediators. It is produced as three isopeptides (ET-1 to ET-3) originating from larger propeptides. The propeptides are transformed to active endothelin by endothelin-converting enzymes. Different endothelin isopeptides are produced in different tissues. For example, only ET-1 is normally produced by cerebral endothelium. Endothelin production can be upregulated by thrombin, transforming growth factor β1, hemoglobin, and TNFα and can be downregulated by NO and cGMP.

Local mediators and the autonomic nervous system play a significant role in blood flow regulation.

Local mediators do not work in isolation—the net effect on VSMC tone reflects the balance between vasoconstrictor and vasodilator signals, which are also affected by changes in receptor density, presentation, activity, and changes in post-receptor activity.

Endothelial injury reduces the action of some mediators that depend on stimulating NO production.

NO causes vasodilation by activation of VSMC soluble guanylate cyclase, which increases intracellular cGMP.

Prostacyclin causes vasodilation by acting through a VSMC receptor to increase intracellular cAMP, which activates potassium channels, and by increasing endothelial NO production through action at an endothelial receptor.

EDHF is more important than NO for vasodilation of smaller arteries. EDHF has not been fully characterized yet and may represent more than one mediator, depending on the vascular bed.

Endothelin is a potent endothelial-derived vasoconstricting mediator. There are two endothelin receptors on vascular smooth muscle: ET_A and ET_B; the latter receptor is also on vascular endothelial cells where endothelin binding stimulates increased NO production.

To complicate the understanding of its physiologic effects, endothelin can bind to two different vascular receptors, ET_A and ET_B. In vascular smooth muscle, these receptors are coupled to Gq-protein; receptor activation increases inositol triphosphate (IP3), which increases the release of Ca^{2+} from the sarcoplasmic reticulum. Increased intracellular Ca^{2+} concentration causes vasoconstriction. ET_B receptors on vascular *endothelial* cells respond to endothelin by increasing NO production. Studies show that low doses of ET-1 cause vasodilation through endothelial ET_B receptor activation; higher concentrations result in vasoconstriction through activation of VSMC ET_A receptors. The action of endothelin varies based on the vascular bed. For example, ET_A and ET_B receptor blockade does not alter basal cerebral artery tone, suggesting that endothelin has no role in the tonic regulation of the cerebral VSMC, whereas endothelin receptor inhibitors are effective in the management of pulmonary hypertension.

15.2 Potassium Channels

Activation and opening of potassium channels allow potassium to flow out of the cell down its concentration gradient, which removes positively charged ions from within the cell causing hyperpolarization of the VSMC membrane → closure of voltage-dependent Ca^+ channels → decreased intracellular Ca^+ concentration → smooth muscle relaxation. The resting VSMC membrane potential has been measured in vitro to range from −40 to −70 mV in different vascular beds. Minimal changes in the resting potential lead to significant changes in smooth muscle tone and arterial resistance. There are four main potassium channels that have been identified as part of the regulatory mechanism of regional blood flow:

- *ATP-sensitive potassium channels* (K_{ATP}) are regulated by intracellular concentrations of ATP. Decreased ATP concentration causes dissociation of ATP from the channel, which results in channel opening. Several mediators cause hyperpolarization of the arterial smooth muscle membrane through this mechanism: adenosine, cAMP, opioids, calcitonin gene-related peptide, vasoactive intestinal peptide, and EDHF are only some of the identified mediators. Nitric oxide does not act through activation of ATP-sensitive potassium channels.

  ATP-sensitive potassium channels also have been implicated in vasodilation induced by hypoxia, acidosis, and hypotension where ATP production is compromised. The effect of these channels in the regulation of basal arterial tone is less clear and demonstrably less crucial.
- *Calcium-dependent potassium channels* (K_{ca+}) are activated by increased intracellular calcium ion concentrations. Their activity increases with membrane depolarization. As with the K_{ATP} channels, many mediators have been implicated in the activation of K_{ca+} channels. Isoproterenol and cAMP increase their activity. cAMP-mediated K_{ca+} channel activation is thought to play a significant role in basal vascular tone regulation. Activation of the same channels by NO and cGMP may play a significant role in the microcirculation.
- *Voltage-dependent potassium channels*, also called delayed rectifier potassium channels, open when membrane depolarization occurs. Their role is generation of an outward current that leads to repolarization. They seem to be part of the control system regulating vascular tone. Their exact role in regulating the circulation in different vascular beds is currently unclear.

- *Inward-rectifier potassium channels* open with membrane hyperpolarization, and it is believed that they play a role in maintenance of basal tone and membrane resting potential. The role of these channels needs to be further investigated, but it was recently shown that elevations of extracellular potassium activate the channels and lead to vascular relaxation. The role of the inward-rectifier potassium channels may be more important than initially thought; for example, they may play a significant role in neurovascular coupling. Specifically, when neurons are activated and depolarized, slight increases in extracellular potassium concentrations may, through the inward-rectifier potassium channels, cause direct smooth muscle relaxation and hence cerebral arteriole vasodilation, which helps match blood flow to increased neuron metabolic activity.

Activation of ATP-sensitive potassium channels causes hyperpolarization of the VSMC membrane → closure of voltage-dependent Ca^+ channels → decreased intracellular Ca^+ concentration → smooth muscle relaxation.

There are four types of K^+ channels that play a role in VSMC tone: (1) ATP-sensitive potassium channels, (2) calcium-dependent potassium channels (3), voltage-dependent potassium channels, and (4) inward-rectifier potassium channels.

15.3 Temperature Regulation of Blood Flow

Since the human body can only function within a narrow range of core temperatures, blood flow and vascular tone are also influenced by temperature. Metabolic expenditure is inversely related to body temperature within the normal physiologic temperature range. When the body needs to increase its core temperature, significant peripheral vasoconstriction is seen in all tissues in contact with ambient colder temperature in order to limit further heat loss. Blood flow is shifted to the core of the body away from the skin to reduce radiant and convective heat loss and maintain internal vital organ temperature for normal function.

Temperature plays a significant role in blood flow regulation either directly by reducing or increasing heat loss through the cutaneous vascular bed or indirectly by altering the metabolic rate.

15.4 Blood Flow and Oxygen Consumption

Although clinicians think about blood flow in terms of L/min/m^2 for cardiac index (CI), organ blood flow is often expressed in units of mL/min/100 g of tissue. To put organ blood flow into context with the overall cardiac output, it is helpful to recognize that weight-based cardiac output changes markedly across the pediatric age range compared with the relatively stable blood flow measured per body surface area (i.e., neonate CI is 4–5.5 L/min/m^2 vs adults at 2.5–4 L/min/m^2). When expressing this flow per 100 g, however, the overall cardiac output is ~24 mL/min/100 g in a neonate, falling to ~14.7 mL/min/100 g in a 6–7-year-old and to ~8.7 mL/min/100 g in a 70 kg adult.

Note that since skeletal muscle represents 45% of body mass, the maximal blood flow in skeletal muscle represents a huge increase in cardiac output due to increased oxygen demand. Similarly, the skin has the potential of becoming an important source of increased blood flow since it represents 7.5% of body weight and can increase flow over 18-fold from baseline.

Many organs receive blood flow well in excess of their metabolic demand, whereas other organ beds extract a larger than normal fraction of delivered oxygen. Overall oxygen extraction is normally approximately 25% of the delivered oxygen; this can be remembered if you recall that one of the four oxygen molecules bound to hemoglobin is normally consumed in the microcirculation. Oxygen extraction is measured as the arteriovenous O_2 content difference (mL O_2/100 mL of blood). The values for organs are seen in Table 15.2. As noted, the heart has high oxygen extraction at baseline, whereas other organs, such as skeletal muscle or the splanchnic circulation, can maintain adequate tissue oxygen by extracting a greater percentage of the delivered oxygen when blood flow is low. On average, about ~5 mL O_2/100 mL of blood is extracted (22–30% across most organs).

Table 15.2 Resting and maximal blood flow in various organs and normal oxygen extraction across adult organ beds ($AVDO_2$). The proportion of blood flow as a percentage of cardiac output is presented for adults; brain blood flow in infants will be a higher percentage of cardiac output. Flow is measured in mL/100 g/min

Organ	Resting blood flow (mL/100 g/min)	Maximal blood flow (mL/100 g/min)	Magnitude of increase from resting to maximal	Percentage of resting cardiac output	$AVDO_2$ mL of O_2 per 100 mL blood (O_2ER)
Brain	54	140	2.6-fold	14	6 (31%)
Heart	70	390	5.5-fold	4.5	11 (57%)
Liver/splanchnic[a]	98	250	2.55-fold	25	5 (26%)
Kidney	310	390	1.25-fold	20	1.5 (7.8%)
Muscle	4	18	4.5-fold	21	5 (26%)
Skin	8	150	18.75-fold	7.5	2 (10%)

$AVDO_2$ is the arteriovenous oxygen content difference (mL O_2/100 mL of blood) and O_2ER (oxygen extraction ratio) is the percentage of oxygen extracted from arterial blood assuming a hemoglobin concentration of 14 g/dL, 100% arterial oxygen saturation, and PaO_2 of 100 mm Hg

[a]Liver/splanchnic flow represents hepatic artery and portal venous blood flow to the liver; the latter represents most of the splanchnic blood flow

15.5 Mechanisms of Regional Blood Flow Regulation during Stress and Pathological Conditions

When thinking about blood flow and its organ system regulation, it may help to consider how a municipal water system delivers water. The water tower creates the driving pressure, similar to the heart's pumping function. When someone opens a faucet, water flows through that faucet based on the pressure head. If too many faucets are open at the same time, as may be seen with sepsis, then the pressure and flow at each faucet in the water system falls. Furthermore, if the water tower is depleted of water, pressure and flow will fall. Similarly, if the capacitance venous system relaxes excessively, the blood return to the heart falls and thus less blood flow and pressure is generated.

The same basic principles (oxygen delivery, local and systemic mediators, and autonomic nervous system) that regulate blood flow during usual physiologic conditions apply during stress.

The driving pressure generated by the heart and the vascular tone in organs determine regional blood flow. If too many vascular beds are dilated, the pressure and flow throughout the circulatory system will fall.

During stress, whether from a critical illness or running a marathon, metabolic demand increases and the autoregulatory mechanisms of blood flow and oxygen delivery act to increase blood flow where it is most needed. The human stress response evolved to help survive threats from predators. Thus, the autonomic stress response is designed to assure that there is adequate blood flow to skeletal muscles to fight or run. Sympathetic nervous system (SNS) activation leads to epinephrine release from the adrenal gland, which acts preferentially at the hormonal β_2-adrenoceptors that are prominent in the skeletal muscle bed. It also acts at cardiac β_1- and β_2-adrenoceptors to increase contractility and heart rate, which increases cardiac output. SNS activation also increases the action at innervated α_1-adrenergic receptors, which are more highly concentrated in the splanchnic, renal, and cutaneous circulations; this helps redirect blood flow from those organs while preserving blood flow to the brain and heart, which have little response to α-adrenergic stimuli.

In addition to autonomic system activation, a host of other mediators are active during stress states, depending on the nature and type of stress. In addition to regulation of regional blood flow by SNS activation and release of various mediators, there are local mechanisms that help maintain blood flow. These local mechanisms vary depending on the organ involved, as detailed in subsequent regional circulation discussions below.

In different pathological states (e.g., cardiogenic or hypovolemic shock, hypertension, diabetes, sepsis), malfunction of different regulatory mechanisms (e.g., endothelial dysfunction with decreased NO production and/or vasodilatory sensitivity) causes impaired oxygen delivery and blood flow to the tissues. The analysis of circulatory regulation during specific pathological states is beyond the scope of this chapter. These mechanisms are discussed in other chapters addressing specific pathological states.

15.5.1 Hemodynamic Coherence and the Microcirculation

In the management of critical illness, attention is often focused on restoring mean arterial pressure (MAP), filling pressures such as the central venous pressure (CVP), and cardiac index (CI). The assumption is that achieving these macrocirculatory endpoints will restore regional organ perfusion. Recent studies using methods to study the microcirculation, however, show that this is not always the case. The term "hemodynamic coherence" was introduced in 2015 to describe this association between the macro- and microcirculations.

For hemodynamic coherence to function properly, the compensatory mechanisms at the macro- and microcirculatory levels should match oxygen delivery to the normally heterogeneous tissue metabolic demand. Thus, activation of the SNS, renin-angiotensin-aldosterone system, local biochemical control mechanisms, and signaling molecules should match oxygen demand to oxygen delivery. Unfortunately, during critical illness or injury, activation of the inflammatory and coagulation system often disrupts or obstructs microvessels with platelets and/or fibrinogen. There also may be localized over- or underproduction of NO, and the membrane receptor and post-receptor signaling pathways may be altered depending on the competitive signals received by endothelial and vascular smooth muscle cells.

Based on studies of the microcirculation in various animal models and during critical illness, four types of microcirculatory alterations are thought to underlie the loss of hemodynamic coherence. These alterations are typically associated with a reduced functional capillary density and thereby the loss of the capacity of the microcirculation to deliver oxygen to the tissues.

1. *Heterogeneity in microcirculatory perfusion* with obstructed capillaries next to perfused capillaries. Sometimes, there are shunts in the microcirculation that allow blood flow to bypass capillaries. This type of disturbance is often seen in sepsis, but also was observed in children on ECMO. The degree of capillary heterogeneity was associated with increased morbidity and mortality. Note that this circulatory abnormality results in reduced oxygen extraction, as seen in patients with sepsis. Thus, reduced oxygen extraction and consumption in tissue beds and organs may not be because cells are unable to extract oxygen; instead, some cells within the microvascular bed receive oxygen well in excess of their metabolic demand while other cells are ischemic.
2. *Hemodilution* reduces oxygen carrying capacity at the capillary level and may increase diffusion distance between capillaries containing red blood

Hemodynamic coherence describes the relationship between the macro- and microcirculations. In critical illness, this relation may be disrupted so that microcirculation may be impaired despite restoration of macrocirculatory parameters. Four types of microcirculatory alteration are thought to underlie the loss of hemodynamic coherence: (1) heterogeneity in microcirculatory perfusion, (2) hemodilution, (3) vasoconstriction/tamponade, and (4) tissue edema, which increases diffusion distance from capillaries.

cells (RBCs) and tissue cells. This abnormality is most often seen in patients undergoing cardiopulmonary bypass with hemodilution.

3. *Vasoconstriction/tamponade*: vasoconstriction reduces RBC flow, *or* increased venous pressure increases hydrostatic pressure impeding (tamponade) microcirculatory flow. The latter may be induced by increased venous vascular resistance or excessive fluid resuscitation. If fluid resuscitation increases venous pressure, this may adversely affect the microcirculation. Studies of microcirculatory flow observed that vasopressors may improve systemic blood pressure, but excess microcirculatory vasoconstriction can impair tissue blood flow. Of note, hyperoxia may be a cause of this type of flow restriction where increased oxygen tension in the blood delivered to tissues is sensed locally as adequate blood flow leading to local vasoconstriction, which may compromise flow to at-risk microcirculation.
4. *Tissue edema increasing diffusion distance*. If capillary permeability is increased, any increase in capillary hydrostatic pressure leads to more interstitial fluid, which may overwhelm the lymphatic system, especially if the right atrial pressure is increased or the inflammatory response has obstructed lymphatic drainage. This mechanism may partly explain the worse outcome observed in the liberal fluid resuscitation group in the randomized trial of conservative versus liberal fluid resuscitation in African children. Microcirculation studies in adults with malaria show that giving fluid to improve cardiac output did not improve microvascular obstruction and instead promoted tissue edema in the lungs and kidney.

Ideally, clinicians will be able to resuscitate patients by assuring adequate perfusion to the microcirculation, but readily available and noninvasive bedside tools to reliably monitor microvascular blood flow and metabolic balance in the tissues are not yet available. Clinicians may suspect ongoing abnormalities in microcirculatory flow when the patient has restoration of macrocirculatory goals, but there are ongoing acidosis, lactate production (or slow lactate clearance), and evidence of worsening organ dysfunction.

15.6 Coronary Circulation

15.6.1 Anatomy, Histology, and Physiology

Humans have two coronary arteries. The right coronary artery supplies the posterior descending artery in ~70% of the population, which represents a right dominant circulation.

The human heart is supplied by two main coronary arteries. The left coronary artery gives rise to two major branches, the left anterior descending and the left circumflex artery. The left coronary artery mainly supplies the left atrium and the anterior, septal, and lateral walls of the left ventricle. The right coronary artery mainly supplies the right atrium and the right ventricle as well as the posterior septal and inferior left ventricular territories in 85% of the population. By convention, the artery that supplies the posterior third of the interventricular septum—the posterior descending artery—determines the coronary dominance. In ~70% of the population, the right coronary supplies the posterior descending coronary artery; in ~10%, this artery is supplied from the left circumflex, and in ~20% of the population, it is provided by both coronary arteries (Fig. 15.1).

The heart is a highly aerobic organ that needs continuous inflow of oxidation substrates to generate ATP, as it cannot tolerate anaerobic metabolism for prolonged periods. The baseline oxygen consumption of the myocardium (MVO_2) is high compared to most other organs; it ranges from 8 to 15 mL/min/100 g compared with lower basal oxygen consumption in other organs as

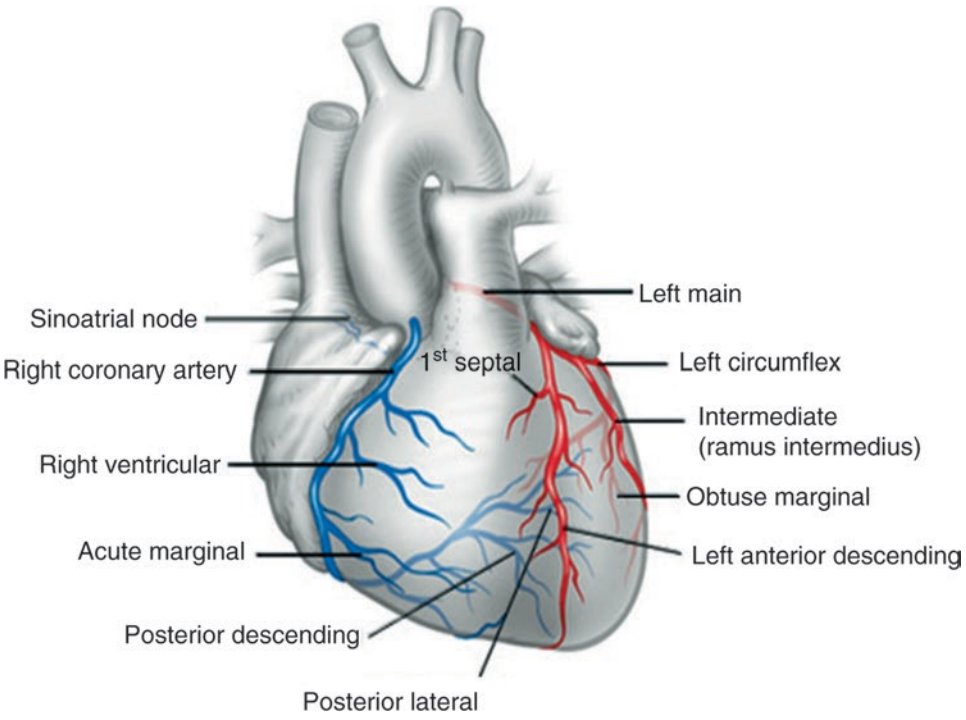

Fig. 15.1 Typical anatomy of the coronary arteries in a human heart. A right dominant circulation is shown: the posterior descending coronary artery (PDCA) is provided by the right coronary artery, which occurs in ~70% of the population. In ~10% of the population, the PDCA is provided by the left circumflex artery (left dominant system), and in ~20%, both coronary arteries (codominant system) supply the PDCA

Table 15.3 O_2 consumption in various adult organ systems

Organ system and state	O_2 consumption (mL O_2/min/100 g)
Resting heart	8
Arrested heart	1.5
Heart during heavy exercise	70
Brain	3
Kidney	5
Skin	0.2
Resting muscle	1
Contracting muscle	50

The table demonstrates the wide range in O_2 consumption in the heart and skeletal muscle based on metabolic demand

summarized in Table 15.3. In the arrested heart, MVO_2 immediately decreases to ~10% of normal metabolism (~1.5 mL/min/100 g). That is true for the fibrillating heart as well, where there is no organized contractile function and no wall stress. Conversely, MVO_2 and thus coronary blood flow can increase ~9-fold during heavy exercise.

Energy consumption of the myocardium is determined by the following factors: myocardial wall stress, heart rate, and myocardial contractility. Direct measurement of myocardial wall stress or MVO_2 is difficult but can be estimated by the pressure-rate product, which is the systolic blood pressure times the heart rate. Clinical studies show that the pressure-rate product is closely related to MVO_2 and myocardial wall tension. For the heart to meet its energy requirements, the coronary blood flow must be capable of rapid adjustments.

Basal oxygen consumption varies widely across organ systems and may need to increase up to 50-fold with increased metabolic demand

15.6.2 Local Regulation of Coronary Blood Flow

The normally beating heart is perfused via coronary blood flow mainly during diastole (Fig. 15.2). The elastic properties of the aorta, which acts as a reservoir, allow for a constant relatively uniform coronary blood flow throughout diastole. Coronary perfusion pressure (CPP) is defined as the diastolic blood pressure minus right atrial pressure, since most coronary blood drains into the coronary sinus located in the right atrium. Thus, during cardiopulmonary resuscitation (CPR), cardiac perfusion occurs mainly during the decompression phase of chest compression when the diastolic aortic pressure is higher than the right atrial pressure creating a positive CPP gradient.

Unlike flow through the left coronary artery, right coronary artery blood flow also occurs during systole because RV intracavitary pressure and wall stress is significantly lower than aortic blood pressure throughout the entire cardiac cycle, unless severe right ventricular hypertrophy exists due to pulmonary hypertension or pulmonary stenosis (Fig. 15.2).

Coronary perfusion of the left ventricle occurs mainly during diastole; the driving force for coronary blood flow is determined by the coronary perfusion pressure, which equals diastolic blood pressure minus right atrial pressure.

The major coronary arteries are conductance vessels and do not cause a pressure drop throughout their course to the epicardium (unless a blockage exists). The size of the epicardial coronary arteries ranges from 0.3 to 6 mm in caliber. Coronary circulation resistance is generated from the arterioles (resistance vessels) with diameters ranging from 10 to 200 μm. The resistance vessels give rise to an enormous number of capillaries that form a very dense network of approximately 3000–3500 capillaries per square millimeter, which maximizes the capillary to myocardial cell ratio and couples the supply of oxygen to demand. If the myocardium hypertrophies, the density of the capillary network decreases. One of the most remarkable physiologic properties of the coronary microcirculation is its recruiting capability. Under normal conditions, many capillaries are closed by increased tone of the precapillary sphincter. When myocardial oxygen demand increases, relaxation of the precapillary sphincter drops the resistance and increases the capillary density and thus blood flow per 100 g of myocardial tissue, which allows the heart to achieve the

Epicardial coronary vessels are conductance vessels that do not cause a significant pressure decrease even during maximal blood flow. Arterioles with diameters of 10–200 μm are the resistance vessels.

Capillary recruitment is a very efficient mechanism to improve oxygen delivery to the myocardial tissue when there is increased metabolic demand or when flow is impeded by epicardial vessel obstruction.

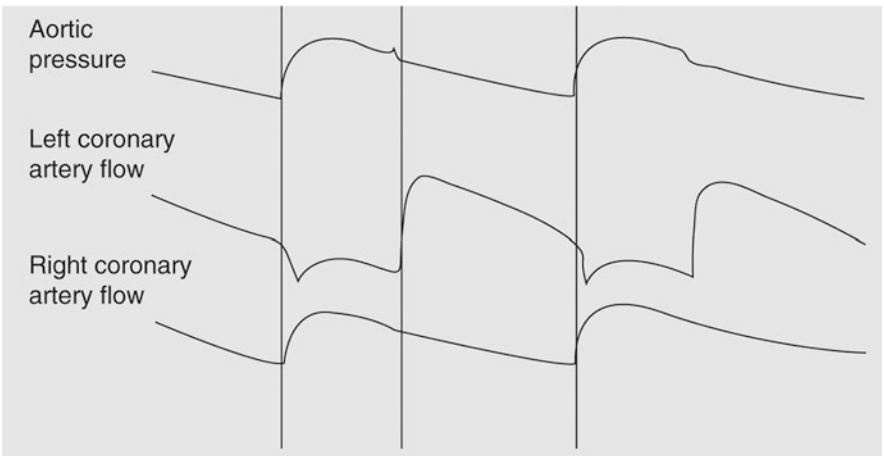

Fig. 15.2 During systole and diastole, blood supplied by the coronary vessels is exposed to changing myocardial pressures. During isovolumic contraction of the left ventricle (preejection), myocardial tissue compression causes flow in vessels supplied by the left coronary artery to fall to zero or even become retrograde. With the onset of diastole, removal of the compression results in a large inflow into these vessels early in diastole. Flow parallels diastolic aortic pressure during the remainder of the cycle. *In the normal right ventricle, flow occurs during systole because systolic myocardial pressures in the wall of the right ventricle do not exceed aortic pressure*. The flow profile in the right ventricle closely resembles the pressure profile in the aorta

wide range of oxygen delivery to meet changing metabolic demand as noted in ◘ Tables 15.2 and 15.3.

The coronary circulation resistance is regulated mainly by the small arterioles with a diameter below 30 μm. Myogenic regulation by smooth muscle control occurs at intermediate arteries with diameters between 30 and 60 μm. Larger arteries are the site of flow-mediated dilation. When the small arterioles dilate, vascular resistance decreases and coronary blood flow increases. This downstream drop in pressure causes the larger vessels' smooth muscle to relax in order to avoid collapse, further decreasing resistance. The increased flow at the largest epicardial vessels causes an increase in shear stress, which induces epicardial vessel relaxation.

Coronary circulation resistance is mainly determined by the smallest arterioles with diameter <60 μm. Arteriolar dilation increases shear stress of the epicardial arteries, which induces dilation of the conductance vessels.

15.6.3 Specific Determinants of Coronary Blood Flow

15.6.3.1 Transmural Distribution of Coronary Blood Flow

Subendocardial tissue experiences greater pressure than the epicardium during systole so that local blood flow occasionally ceases during systole. During diastole, the ratio of endocardial to epicardial flow is about 1.5:1 but averages for the entire cardiac cycle to about 1.25:1. During resting conditions, the endocardium's energy requirements are approximately 20% higher than the epicardium so that the increased subendocardial blood flow matches the increased metabolic demand.

Endocardial muscle has higher oxygen demand and therefore receives ~25% more blood flow during the cardiac cycle compared with the epicardial myocardium. Endocardial blood flow may cease during systole, so diastolic endocardial blood flow is ~50% higher than epicardial flow.

The subendocardial tissue is more vulnerable to ischemia for the aforementioned reasons. A total decrease of regional coronary blood flow by 40% due to an epicardial coronary stenosis causes the normal ratio of endocardial to epicardial blood flow of 1.25 to drop to 0.4. This flow redistribution from the endocardium to epicardium is exaggerated during exercise, tachycardia, stress, or by the use of potent arteriolar vasodilators such as adenosine or dipyridamole. This phenomenon has been called coronary steal. Elevated left ventricular diastolic pressures and left ventricular hypertrophy further decrease the perfusion ratio between the endocardium and the epicardium. An increase in mean aortic pressure can improve endocardial perfusion and bring the ratio closer to normal. This is because the endocardial arterioles are maximally dilated and, therefore, flow is mainly pressure dependent. Reducing myocardial oxygen consumption by β-adrenoceptor inhibition, which decreases metabolic demand, helps restore the balance between coronary blood flow and oxygen consumption. If a nonselective β-blocker is used, the inhibition of peripheral vascular β_2-adrenoceptors increases systemic vascular resistance and thus diastolic blood pressure, which improves CPP, but increases afterload and thus ventricular wall stress.

When an epicardial arterial stenosis exists, the endocardial vessels within the distribution territory are maximally dilated, and therefore blood flow is mainly dependent on diastolic arterial pressure.

15.6.3.2 Metabolic Regulation of Coronary Blood Flow

Coronary blood flow regulation is very closely related to the metabolic need of the myocardium, which is the main regulator of local blood flow. Since there are limited glycogen reserves to support anaerobic ATP production, the heart requires a continuous supply of oxygen to generate ATP aerobically to meet its substantial metabolic demand. Any increase in cardiac metabolic requirements leads to a near instantaneous decrease in coronary resistance. Arterial occlusion for even 1 second leads to a reactive increase of coronary blood flow, called *reactive hyperemia.* Many agents and mediators have been implicated in this phenomenon, but the specific mechanism(s) remains uncertain. Adenosine, ATP, and nitric oxide (NO) have been studied extensively as mediators of reactive hyperemia.

Adenosine, ATP, and nitric oxide are considered important flow regulation mediators.

Cardiac muscle uses fatty acids (~60–70%) and carbohydrates (~30–40%) for energy.

Oxygen extraction is maximal, and the coronary sinus oxyhemoglobin saturation is ~30% at rest.

The major cardiac metabolic substrates for energy are fatty acids (60–70% of energy production) and carbohydrates (glucose, lactate, and ketones; ~30–40%). To meet its high metabolic demand, the heart extracts 65–70% of the delivered oxygen unlike other organs that extract only 20–30% of delivered oxygen. Thus, the coronary sinus venous oxyhemoglobin saturation is ~30% at rest. The heart is able to extract oxygen even at low arterial partial pressure of oxygen.

Adenosine and ATP are powerful coronary dilators that are considered important mediators of local metabolic regulation. Adenosine and ATP concentrations increase at times of an imbalance in the supply-to-demand ratio for oxygen; the rise in the interstitial concentration of adenosine parallels the increase in coronary blood flow. Although adenosine meets most of the criteria for a metabolic regulator of coronary blood flow, inhibition of the adenosine receptor does not always reduce the magnitude of the hyperemia in response to metabolic stimuli in animals or humans. Thus, adenosine is not the only mediator responsible for this phenomenon.

Nitric oxide (NO) is also a mediator of coronary blood flow regulation. Adenosine acts through endothelial receptors to stimulate NO production, which also increases in response to tissue hypoxia and flow-mediated increased endothelial shear stress. NO inhibition decreases the magnitude of coronary vascular relaxation in response to metabolic stress. NO is mainly responsible for the late sustained phase of reactive hyperemia.

A host of other mediators have been implicated in local vascular tone control including vasodilator (prostacyclin) and vasoconstrictor (thromboxane) prostaglandins, natriuretic peptides, bradykinin, endothelin, angiotensin II, and histamine. As noted previously, these mediators create the potential for complex effects on local vessel tone, but metabolic factors are likely the predominant determinants of myocardial blood flow. Inhibition of adenosine, nitric oxide, and K^+ channels together completely blocks the increase of coronary blood flow during exercise in dogs. Since NO is derived from the endothelium, an intact endothelium is important; endothelial injury and dysfunction reduces NO production and often leads to increased local vascular tone, which increases the risk of ischemia.

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Since myocardial oxygen demand is the main determinant of coronary blood flow, it is helpful to recognize differences in oxygen demand related to the different types of work that the ventricle performs. In the heart, work is related to the volume of blood pumped and the pressure that needs to be generated to perform the pumping function (i.e., volume × pressure). Left ventricular stroke work index (LVSWI) is defined as SI × (MAP-LAP) × 0.0136 g-m/m^2, where SI is the stroke index (mL/beat/m^2), MAP is the mean arterial pressure, LAP is the left atrial pressure (which may be estimated by the pulmonary artery occlusion pressure), and the factor converts the parameter into the units noted.

For a given degree of ventricular work, the myocardial oxygen demand is significantly lower when the ventricle is performing volume rather than pressure work. This difference in oxygen demand is used clinically to improve cardiac output in patients with reduced ventricular pumping function by lowering vascular resistance.

Note that LVSWI increases when either or both SI or the MAP-LAP component increases. However, the oxygen demand for a given degree of ventricular work is *not* constant. If the patient's systemic vascular resistance increases, oxygen consumption increases much more than if the SVR decreases and SI increases to achieve the same level of LVSWI. Thus, the metabolic demand of the heart is lower when it is doing volume rather than pressure work. This is observed clinically in an infant who tolerates a large ventricular septal defect where the right ventricle can pump three to four times the amount of blood pumped by the left ventricle compared with the infant with pulmonic stenosis where the increased pressure work results in heart failure. The ventricle prefers to do volume work pumping into a low vascular resistance system rather than pressure work trying to pump into a vascular system with high resistance or pumping across a fixed obstruction.

15.6.4 Adrenergic Control of Coronary Blood Flow

For the heart to maintain a sustained increase in coronary blood flow during prolonged periods (e.g., exercise), there is a need for positive feedback mechanisms that can alter the hemodynamics in a way that promotes coronary blood flow. Local metabolic control is inadequate to explain the phenomenon, and all the substances (e.g., NO, adenosine, and K^+_{ATP} channels) that have been tested alone or in combination could not account for the changes observed during exercise. However, during rest, NO and K^+_{ATP} channels contribute significantly to the maintenance of vascular tone.

NO, adenosine, and K^+_{ATP} channels contribute to the maintenance of coronary vascular tone during rest but cannot account for all the changes seen during exercise.

Both sympathetic and parasympathetic nerves enervate the coronary arteries, suggesting that they can regulate coronary blood flow. Activation of β_2-adrenoceptors increases flow, whereas activation of α_1-adrenoceptors causes vasoconstriction. These actions, however, can be overcome based on changes in metabolic demand. For example, coronary vasoconstriction is not observed when high doses of epinephrine are given during cardiac arrest. In addition, critical illness may alter the response to sympathetic stimulation; for example, adults with septic shock have increased coronary blood flow despite vasodilated sepsis with low diastolic blood pressures.

When the sympathetic nervous system is activated during exercise or illness-related stress, contractility, heart rate, and cardiac output increase. Systolic blood pressure rises, but often diastolic blood pressure falls due to increased blood flow to skeletal muscles mediated by reduced systemic vascular resistance. These physiologic changes increase myocardial metabolic demand and thus coronary blood flow, which is achieved through the effects of local metabolic mediators causing coronary vasodilation. In experimental models, it is difficult to isolate the local metabolic effects from the adrenergic effects.

15.6.4.1 α-Adrenergic Effects on Coronary Blood Flow

Direct α-adrenergic activation with simultaneous β-adrenergic blockade decreases coronary blood flow that can be reversed with α-adrenergic blockers. In addition, at a given level of oxygen consumption, α-adrenergic blockade causes higher coronary blood flow and lower coronary arterial resistance.

In the systemic circulation, excessive α-adrenergic-mediated vasoconstriction increases systemic vascular resistance, which increases afterload on the ventricle. Increased diastolic pressure increases the compressive forces especially on the subendocardial tissues, which can result in subendocardial ischemia. In addition, as noted above, increased afterload increases myocardial oxygen demand more than doing volume work. Thus, even though direct α-adrenergic stimulation is expected to cause coronary vasoconstriction, the increased myocardial metabolic demand by the increased systemic afterload typically increases coronary blood flow, although the flow increase may be limited by the effects of increased α-adrenergic activity on the coronary circulation.

15.6.4.2 β-Adrenergic Effects on Coronary Blood Flow

Activation of β_2-adrenoceptors causes direct coronary vasodilation. Experimentally, the effect is very difficult to separate from metabolic vasodilation due to locally produced mediators.

β_2-adrenoceptor activation causes coronary vasodilation and increased blood flow.

The effects of β-adrenoceptor stimulation on heart rate and cardiac contractility further augment coronary blood flow due to increased metabolic demand. In summary, the effects of adrenergic stimulation on the coronary circulation is determined by both direct actions on the coronary vessels and indirect effects mediated by changes in heart rate, contractility, and afterload.

15.6.5 Coronary Blood Flow during CPR

During cardiac arrest (asystole or ventricular fibrillation (VF)), coronary flow ceases when the mean aortic pressure equals the mean central venous pressure. Usually that occurs after 3–5 min. During the electrical phase of VF cardiac arrest (the first 4–5 min), biphasic or monophasic shocks have a high success rate. In the circulatory phase of VF arrest (5–10 min), effective CPR to supply the heart with the energy needed for the reinstitution of an organized rhythm is required prior to successful shocks.

During CPR, coronary perfusion occurs during the decompression phase, and a CPP of at least 15 mm Hg is needed for successful resuscitation.

During chest compression, both the aortic pressure and the right atrial pressure increase; indeed, since the right atrium is located just below the sternum, often the right atrial pressure exceeds aortic pressure during active compression. During the decompression phase, the right atrial pressure falls faster and lower than the aortic pressure, creating the pressure gradient that perfuses the heart with oxygenated blood. The inability to achieve a CPP above 15 mm Hg during CPR is a poor prognostic factor for a successful outcome.

15.6.6 Effects of Acidosis, Hypocapnia, and Hypercapnia on Coronary Blood Flow

Coronary arteries vasodilate during systemic acidosis accompanied by a decreased response to vasoactive medications. The vasodilation occurs predominantly due to the inability of the regulatory vascular mechanism to distinguish between local and systemic acidosis. Interestingly, when myocardial blood flow was measured in humans during hypo- and hypercapnic conditions, there was an increase in blood flow only during hypercapnia, but no changes were observed during hypocapnia. Respiratory acidosis has complex effects; in intact (i.e., non-anesthetized) animals, an acute respiratory acidosis is a potent stimulus for sympathetic nervous system activation with increased epinephrine concentrations resulting in increased myocardial oxygen demand. This will increase coronary blood flow *independent* of any direct effect of pCO_2 on coronary vessels.

Acidosis causes a decrease in the response of the coronary arteries to vasoconstrictors. Hypercapnia but not hypocapnia alters coronary blood flow, likely due to systemic activation of the SNS.

The normally high degree of oxygen extraction by the heart and low coronary sinus pO_2 are also accompanied by an increased pCO_2 in coronary blood. At baseline, myocardial tissue pCO_2 is increased and rapidly rises during ischemia. During severe ischemia or cardiac arrest, intramyocardial pCO_2 rises rapidly above 100 mm Hg with an accompanying fall in pH; tissue pCO_2 in excess of 300 mm Hg was documented in animal arrest models. Giving sodium bicarbonate in this setting simply generated higher myocardial tissue pCO_2 levels without improving myocardial tissue pH, illustrating the ineffectiveness of attempting to correct myocardial tissue acidosis by giving sodium bicarbonate.

Hypercapnia has important systemic effects mediated by activation of the SNS that increases myocardial oxygen demand and likely overcomes its direct effects on coronary vascular tone.

Giving bicarbonate to correct acidosis during cardiac arrest likely worsens tissue acidosis by increasing local pCO_2 production, which lowers rather than improves pH.

15.7 Cerebral Circulation

15.7.1 Anatomy and Histology

The human brain is a metabolically active organ that receives ~25% of the cardiac output via the carotid and vertebral arteries. The circle of Willis helps ensure that in the case of unilateral traumatic injury or occlusion of one carotid

or vertebral artery, both hemispheres and the brainstem can maintain blood flow. The circle of Willis gives rise to six main arteries that travel superficially over the brain across the subarachnoid space. From these main arteries, superficial arteries penetrate into the brain parenchyma and branch into arterioles. As the arteries become smaller, the smooth muscle cell layer becomes thinner until it disappears at the capillary level. The Virchow-Robin space surrounds the penetrating arteries; that space disappears as the arterioles penetrate deeper into the cerebral tissue. On the outer side of the Virchow-Robin space, there is the *glia limitans* membrane formed by astrocytes. The capillary density is not uniform in the brain and depends on the location and metabolic activity of the area. The capillary consists of an endothelial cell layer, pericytes, and the capillary basal lamina. The foot projections of the astrocytes are attached on the lamina. The cerebral capillaries are unique since they are not fenestrated and instead have tight junctions forming the blood-brain barrier (BBB).

Endothelial cells play a crucial role in regulating vascular tone by releasing vasoactive mediators such as NO, free radicals, prostacyclin, and endothelin. Pericytes have contractile properties and participate in the control of capillary size.

The brain receives ~25% of the cardiac output. The circle of Willis provides additional security for brain perfusion. Even with total occlusion or trauma of one carotid artery, blood supply to the brain is not significantly jeopardized.

15.7.2 Cerebral Circulation Autoregulation

The normal human brain can maintain a reasonably constant cerebral blood flow (CBF) over a large range of cerebral perfusion pressures (CePP; MAP minus intracranial pressure (ICP)). The normal autoregulatory range for CePP in adults is 50–150 mm Hg (or MAP of 60–160 mm Hg, assuming ICP is 10 mm Hg); a similar range was found in infants and young children. Constant CBF is achieved by altering the vascular resistance (Fig. 15.3). There are four proposed mechanisms for cerebral autoregulation: (1) myogenic, the intrinsic ability of vessels to dilate or constrict in response to changes in transmural wall pressure; (2) neurogenic, mediated by innervation of cerebral vessels; (3) metabolic, likely the main mechanism where changes in tissue pO_2, pCO_2, adenosine, and other mediators affect vascular tone; and (4) endothelial, production of either vasodilating (e.g., NO, prostacyclin) or vasoconstricting (e.g., endothelin) mediators to alter vascular tone.

Due to the functional and anatomical proximity and interrelation of cerebral arteries with neurons and glial cells, the term "neurovascular unit" is used to describe the unity of this structure (Fig. 15.4).

The superficial cerebral arteries penetrate into the parenchyma and give rise to arterioles. The smooth muscle layer progressively becomes thinner until it disappears at the capillary level.

The capillaries are unique since they are not fenestrated and instead have tight junctions forming the blood-brain barrier.

The brain can maintain a reasonably constant cerebral blood flow over a wide range of cerebral perfusion pressures (50–150 mm Hg in adults), by altering the vascular resistance. There are four proposed mechanisms for cerebral autoregulation: (1) myogenic, (2) neurogenic, (3) metabolic (likely the main mechanism), and (4) endothelial.

Neurovascular unit describes the functional unity of arterioles, neurons, and glial cells.

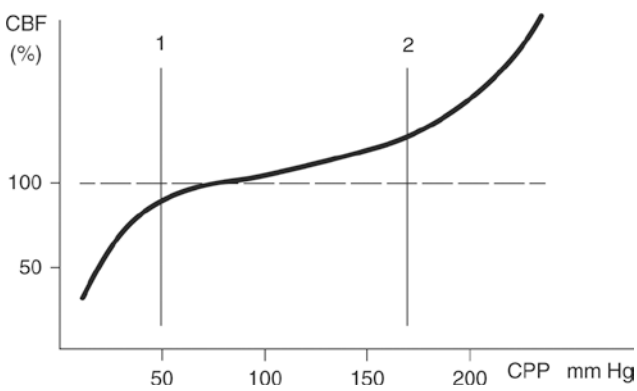

Fig. 15.3 Dependence of total cerebral blood flow (CBF) on cerebral perfusion pressure (CPP). 1 and 2 are the lower and upper limits of cerebral autoregulation, respectively

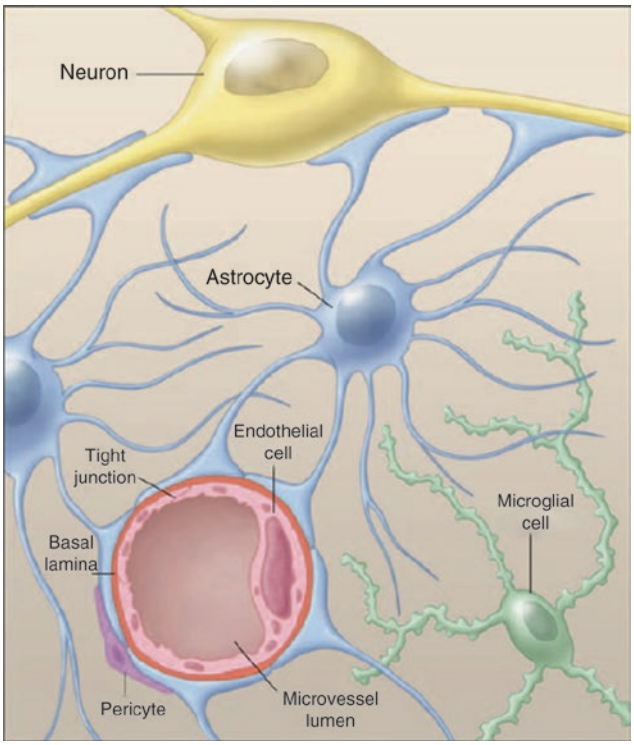

Fig. 15.4 Diagram depicting the neurovascular interface including neurons, astrocytes, microglial cells, and cerebral microvessels. Together with the basal lamina matrix, astrocytic end feet, and pericytes, endothelial cells build the blood-brain barrier

The blood-brain barrier is absent at the choroid plexus.

The restrictive BBB likely blunts the response of CBF to systemic humoral stimuli. With brain injury, the BBB may be disrupted and circulating mediators may then act on neuronal receptors changing metabolic demand and thus blood flow. In the choroid plexus, the BBB is absent so that the effects of systemic stimuli can be observed (e.g., vasopressin causes significant local vasoconstriction).

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15.7.3 Hypoxia and Carbon Dioxide–Related Cerebral Autoregulation

Hypoxemia leading to tissue hypoxia and hypercapnia are two potent stimuli causing vasodilation, which increases CBF. The mechanism of hypercapnia-induced vasodilation is by alteration of tissue pH rather than sensing the absolute pCO_2 value. This has important clinical implications: acute changes in pCO_2 produce rapid changes in cerebral vascular tone, but as renal mechanisms restore the arterial and extracellular pH toward normal by increasing or decreasing the bicarbonate concentration, the initial cerebral vascular effect following a change in pCO_2 is lost over time.

CBF increases significantly with acute hypercapnia, which causes hyperemia. The effect lasts a few hours until the cerebral extracellular pH is corrected by the kidney.

Acute changes in $PaCO_2$ values between 20 and 80 mm Hg change CBF by 1–2 mL/100 g/min for each 1 mm Hg change in $PaCO_2$. The change in CBF is related to the normocapnic CBF; when blood flow is increased, the relative response to hypocapnia is increased. Cerebral blood volume changes to $PaCO_2$ are similar to changes in CBF, but the relative change is less marked. During hypotension, the flow autoregulation response to changes in $PaCO_2$ is lost, whereas untreated hypertension does not affect the response of the cerebral circulation to changes in $PaCO_2$. Hypothermia reduces metabolic demand; thus, normocapnic CBF and the CBF response to changes in $PaCO_2$ are reduced.

During profound hypotension, pCO_2-related autoregulation is lost. Hypothermia reduces metabolic demand and thus CBF and the response to pCO_2 changes.

When ICP is increased, acute hyperventilation can reduce ICP and improve CePP as long as the hyperventilation does not adversely affect systemic venous return. Unfortunately, there is accumulating evidence that therapeutic hyperventilation with hypocapnic goals is harmful, which is likely due to the adverse effects of increased intrathoracic pressure on cardiac output combined with the loss of the pCO_2 effect on CBF over time, as noted above. Thus, current recommendations are to reserve hyperventilation for the transient treatment of acutely increased ICP that cannot be controlled by other methods.

Hypocapnia-induced cerebral vasoconstriction produces short-term effects which are lost as the kidney restores the pH toward normal. Thus, hypocapnia is used for short-term control of ICP until other control methods can be implemented.

15.7.4 Flow-Mediated Regulation

Large cerebral arteries play a significant role in CBF regulation. The tone of the larger arteries determines the perfusion pressure of the microvasculature. This is necessary to protect the thin-layered arterioles from exposure to high pressures, which could lead to their rupture and destruction. Whenever there is large vessel regulation of the tissue circulation, the phenomenon of a vascular "steal" can occur. To avoid vascular steal, the cerebral circulation has another regulatory mechanism: when one region becomes vasodilated in response to increased blood flow needs, the larger upstream arteries dilate to reduce the perfusion pressure and limit stealing blood from the other regions. Flow-mediated vasodilation has been debated as a control mechanism in other vascular beds, but it is of paramount significance in the cerebral circulation.

Flow-mediated vasodilation of the large arteries as a response to microcirculatory vasodilation reduces the risk of vascular steal from other brain territories.

15.7.5 Cerebral Blood Flow with Brain Injury

With traumatic, inflammatory, or ischemic injury, cerebral autoregulation, especially in the area of injury, may be lost so that changes in CePP produce passive changes in CBF. Unfortunately, there are no readily available methods to assess the effects of manipulating CePP on CBF and tissue oxygenation. Some information is available from the use of near-infrared spectroscopy or the use of brain tissue oxygen sensors. As expected from animal studies, sometimes increasing the CePP improves tissue oxygenation without worsening ICP, and in other patients, increasing CePP exacerbates ICP and worsens tissue oxygenation.

Recent data from experimental animals with traumatic brain injury (TBI) suggest that the responses to increasing CePP may vary due to age or gender differences and the agent used to restore CePP (e.g., comparing dopamine to norepinephrine infusion). Male pigs were found to have more disruption of autoregulation compared with females following TBI. In addition, norepinephrine infusion improved CBF in female animals after TBI but not in males, but norepinephrine improved CBF in both genders of neonatal animals with TBI. This complexity may explain some of the variation in response to treatments to improve cerebral blood flow.

CBF autoregulation may be disrupted after ischemic, inflammatory, or traumatic brain injury.

The best method to improve CePP without worsening ICP is difficult to predict with variation in response observed based on gender and age in experimental animals.

15.8 Pulmonary Circulation

15.8.1 Anatomy, Histology, and Physiology

The lungs have a unique double arterial supply originating from the pulmonary and bronchial arteries. There is also a double venous system consisting of the pulmonary and azygos veins. Pulmonary arteries follow the airway bifurcations for multiple generations (17 branching orders) all the way to the level of respiratory bronchioles. Multiple, additional small branches bifurcate inde-

The lungs have dual arterial supply from the pulmonary and bronchial system.

There are 17 branching orders for the pulmonary arteries.

pendently from the airways and penetrate into the lung parenchyma. At the level of the respiratory unit, the pulmonary precapillary arterioles divide into small capillaries (first-order branches) that flood the alveolar wall and allow for the maximum blood gas exchange surface. The draining vessels from the acini form venules and veins located in the interlobular and interlobar septa. The oxygenated blood drains via the four pulmonary veins into the left atrium.

There are five normal histological types of pulmonary arteries:

(i) Elastic arteries (branch orders 17–13). They consist of adventitial, muscular, and intimal layers. The muscular layer is bounded by internal and external elastic laminae with three or more layers within the muscle layer. The medial thickness is only 1–2% of the external diameter, providing a low resistance to flow.

(ii) Muscular arteries (branch orders 13–3). These smaller vascular structures have a thicker muscle layer relative to their external diameter (2–5%), and there is no internal elastic lamina. Pulmonary arteries and arterioles normally have much less smooth muscle compared with similarly sized systemic arteries.

(iii) Partially muscular arteries (branch orders 5–3). Most 50–100 μm arterioles have a spiral arrangement of smooth muscle fibers, and the surrounding muscle coat is incomplete. Again, the limited muscular coat makes them much more easily distensible and compressible compared with systemic arterioles.

(iv) Nonmuscular arteries (branch orders 5 to 1). They have no elastic laminae. The muscle cells are replaced by a pericyte whose basement membrane fuses with that of the endothelial cell lining.

(v) Supernumerary arteries. These are small relatively thin-walled arteries which branch acutely from the parent vessel starting from the orders of 11–12. About 3 supernumeraries take off between each bifurcation. They have a sphincter at their beginning to provide a pressure "step down" from the larger arteries to the smaller arterioles that are supplied by them. They provide a shortcut for blood supplying the alveoli adjacent to the conduit arteries and bronchi.

There are five histological types of pulmonary arteries: elastic, muscular, partially muscular, nonmuscular, and supernumerary.

The thin walls and relatively small amount of smooth muscle in pulmonary vessels compared with systemic arteries and arterioles of equivalent size have important physiologic consequences. The pulmonary vessels have much lower resistance to blood flow compared with systemic vessels. They are also more distensible and compressible than systemic vessels, which affects pulmonary blood flow under conditions commonly seen in the PICU, such as positive pressure ventilation; changes in alveolar and intrapleural pressure can affect pulmonary vascular resistance (PVR).

The thinned wall arterial vessels in the pulmonary circulation have low resistance to flow and are more easily distended or compressed compared with similar-sized systemic arteries and arterioles.

The normal histologic appearance may be modified by conditions that stimulate arterial muscular hypertrophy and growth, such as high shear states associated with large left-to-right intracardiac shunts. These changes may lead to elevated pulmonary vascular resistance (PVR), increased reactivity to stimuli such as hypoxia and hypercarbia, and eventually fixed pulmonary hypertension.

Increased muscularization of the pulmonary vasculature may be caused by high flow and/or pressure resulting in increased vascular reactivity and increased pulmonary vascular resistance.

The pulmonary capillary network has been described as a channel system where each channel is as long as it is wide and has been pictured as a sheet of blood (one red cell thick) with intervening tissue "posts." This vascular network also has been likened to an underground parking garage. The floor to roof height (capillary width) increases about 3% per cm H_2O rise in capillary pressure and decreases as the lung expands. The capillaries densely surround the ~300 million alveoli in the "mature" lung. The huge number of alveoli results in a potential surface area for gas exchange that is estimated to be between 50 and 100 m^2 in the adult.

The capillary network can be envisioned as an underground parking garage or as a sheet of blood with intervening tissue "posts."

The bronchial arteries arise from the aorta or intercostal arteries and supply the bronchial tree, visceral pleura, lymph nodes, and the walls of larger pulmonary arteries and veins with nutrients. About 2% of the left ventricular output is delivered to the bronchial arterial circulation. Some of the bronchial venous drainage enters the azygos and hemiazygos system, but about 70% supplies the intrapulmonary bronchi and drains into the pulmonary veins, creating a small right to left physiological shunt (approximately 1%). When the bronchial circulation increases significantly in pathological states (e.g., bronchiectasis, congenital cyanotic cardiac malformations), the effect of the desaturated bronchial venous blood on the systemic circulation is magnified and can complicate the clinical picture of those patients. In some cases, the bronchial circulation can increase to 30% of total cardiac output in severe bronchiectasis. Most bronchial arterial supply to the bronchioles forms anastomoses at the capillary level with the pulmonary circulation, but there are also bronchopulmonary anastomoses. In the setting of high left atrial pressures, as in congestive heart failure and mitral stenosis, bronchial flow is diverted from the smaller bronchi and bronchioles to the carinal and major bronchial vessels, increasing the drainage into the right atrium and therefore decreasing the right to left shunt.

Most bronchial arteries anastomose with the pulmonary veins and drain into the left atrium, causing a ~1% anatomic right to left shunt.

15.8.2 Normal Pulmonary Pressures

Systolic pulmonary artery pressure varies between 18 and 25 mm Hg and diastolic pulmonary artery pressure ranges between 6 and 10 mm Hg with a mean pulmonary artery pressure (MPAP) between 10 and 16 mm Hg. There is a significant alteration of the normal physiological values in higher altitudes with lower barometric pressures. A MPAP >25 mm Hg at rest and >30 mm Hg with exercise is considered abnormal and qualifies as pulmonary hypertension.

The mean pulmonary vein pressure is identical to the left atrial pressure (LAP); in the absence of mitral stenosis, LAP is close to the left ventricular end-diastolic pressure of 6–10 mm Hg. The driving pressure (i.e., MPAP – LAP) for the entire cardiac output through the lungs is normally <10 mm Hg, which is <10% of the systemic driving pressure. This is possible because of the extremely low pulmonary vascular resistance, which is approximately one-tenth the systemic vascular resistance. This low resistance permits the use of Glenn shunts and the Fontan repair to achieve pulmonary blood flow in the absence of a pumping ventricle.

The normal mean pulmonary artery pressure is 10–16 mm Hg.

A mean pulmonary artery pressure >25 mm Hg at rest and >30 mm Hg with exercise are criterial for pulmonary hypertension.

15.8.3 Pulmonary Vascular Resistance

Pulmonary vascular resistance (PVR) cannot be measured directly, but is estimated based on Poiseuille's law, which states that for a Newtonian fluid flowing steadily through a nondistensible tube, $P_1 - P_2 = Q * R$, where P_1 and P_2 are the pressures (mm Hg) at the beginning and end of the tube, Q is flow in L/min, and R is resistance. For the pulmonary circulation, the equation is PVR = (MPAP – LAP)/Q. This formula only provides an approximation of the PVR since blood is not a Newtonian fluid, flow is pulsatile rather than continuous, and the "tube" is a distensible set of vessels. The result of this formula results in Wood Units. Multiplying the calculated Wood Units by 79.9 (often rounded to 80) gives the result in metric system units: dynes-s × cm^{-5} units. The normal PVR range in healthy children and adults is 1–3 Wood Units or 80–240 dynes-s × cm^{-5}.

The distribution of PVR differs from that in the systemic circulation where ~70% of SVR is due to the systemic arteries and arterioles. In the pulmonary circulation, ~33% of PVR is due to arteries/arterioles, ~33% is at the capillary level, and, ~33% is due to the pulmonary venous system. These differences

Pulmonary vascular resistance is less than 10% of the systemic vascular resistance, about 1–3 Wood Units or 80–240 dynes-s × cm^{-5}.

have clinical implications; for example, administration of furosemide in patients with pulmonary edema often produces clinical improvement more rapidly than any change in urine output. Data suggests that bolus furosemide stimulates PGE_1 production, which relaxes the postcapillary venules and thus rapidly reduces pulmonary capillary hydrostatic pressure.

The relatively small amount of vascular smooth muscle in the pulmonary arterioles, the low intravascular pressures, and the high distensibility (and compressibility) of the pulmonary circulation lead to extravascular factors having a much greater effect on PVR compared with the systemic circulation. Gravity, body position, lung volume, alveolar and intrapleural pressures, intraventricular pressures, and changes in RV output can all have a significant effect on PVR *without* any alteration of pulmonary arteriole vascular tone.

During exercise or other stresses that increase cardiac output, there is only a small increase in pulmonary artery pressure because of flow-induced distension of compliant vessels and arterial/capillary recruitment of regions of the lungs that were not being perfused at rest.

The high compliance of the pulmonary arterial tree and the ability to recruit unused arterial beds during increased circulating volume is a natural defense mechanism against pulmonary hypertension. At rest, not all of the pulmonary capillaries are perfused, especially those in nondependent lung areas. It is estimated that at rest half to up to two-thirds of pulmonary capillaries are not perfused. During exercise, there is only a small increase in the pulmonary arterial pressure despite increasing cardiac output up to five times normal. This is possible because of the recruitment of pulmonary arterial beds and capillaries that leads to a significant decrease of the pulmonary vascular resistance. In addition, increased flow and a small increase in pulmonary vascular pressure distend perfused arterioles and capillaries, reducing PVR. This reduction in PVR does not require neural or hormonal effects since it can be demonstrated in an isolated pump-perfused ventilated lung. In addition, with exercise there is a small rise in left atrial pressure due to increased blood flow, which leads to distention of the pulmonary venous system with a further decrease in pulmonary resistance (recall that PVR = (MPAP-LAP)/Q).

15.8.4 Hypoxic Pulmonary Vasoconstriction

Unlike the response to hypoxia in the systemic circulation, which is characterized by smooth muscle relaxation and increased localized blood flow, tissue hypoxia *reduces* flow in the pulmonary circulation. This is thought to be a protective mechanism to match pulmonary blood flow at the microcirculatory level to areas of the lung that are being effectively ventilated by restricting flow to areas of the lung that are poorly ventilated. The mechanism of hypoxic pulmonary vasoconstriction is not completely understood. It occurs locally only in the area where there is alveolar hypoxia. Connection to the central nervous system is not required since increased PVR is observed in an isolated lung ventilated with a hypoxic gas mixture perfused using a constant flow pump.

Direct action of alveolar hypoxia on the small pulmonary arteries that are surrounded by the alveoli is mediated by the fall in tissue oxygen tension, which inhibits specific K^+ channels that depolarize the VSMC membrane with subsequent opening of calcium channels that cause smooth muscle constriction.

Systemic arterioles respond to tissue hypoxia with vasodilation.

Although the pO_2 within the pulmonary arteriole is determined by the oxygen saturation of the mixed venous blood entering the pulmonary artery, the small arterioles are surrounded by alveoli, so that the tissue pO_2 on the *outside* of the arteriole falls when the alveolar pO_2 (P_AO_2) decreases. This is consistent with recent data that suggests that tissue hypoxia acts *directly* on the pulmonary vasculature to produce hypoxic pulmonary vasoconstriction. During normoxia, a redox mediator, hydrogen peroxide (H_2O_2), maintains voltage-gated O_2-sensitive K^+ channels in an oxidized *open* state. Hypoxic withdrawal of reactive oxygen species inhibits K^+ channels, thereby depolarizing pulmonary artery smooth muscle cells. This depolarization activates voltage-gated Ca^{2+} channels, enhancing Ca^{2+} influx and promoting vasoconstriction. The role of O_2-sensitive K^+ channels is conserved in most specialized O_2-sensitive tissues, including the ductus arteriosus and carotid body. The unique occurrence of

hypoxic vasoconstriction in the pulmonary circulation relates to the co-localization of an O_2-sensor and O_2-sensitive K^+ channels in resistance pulmonary arteries.

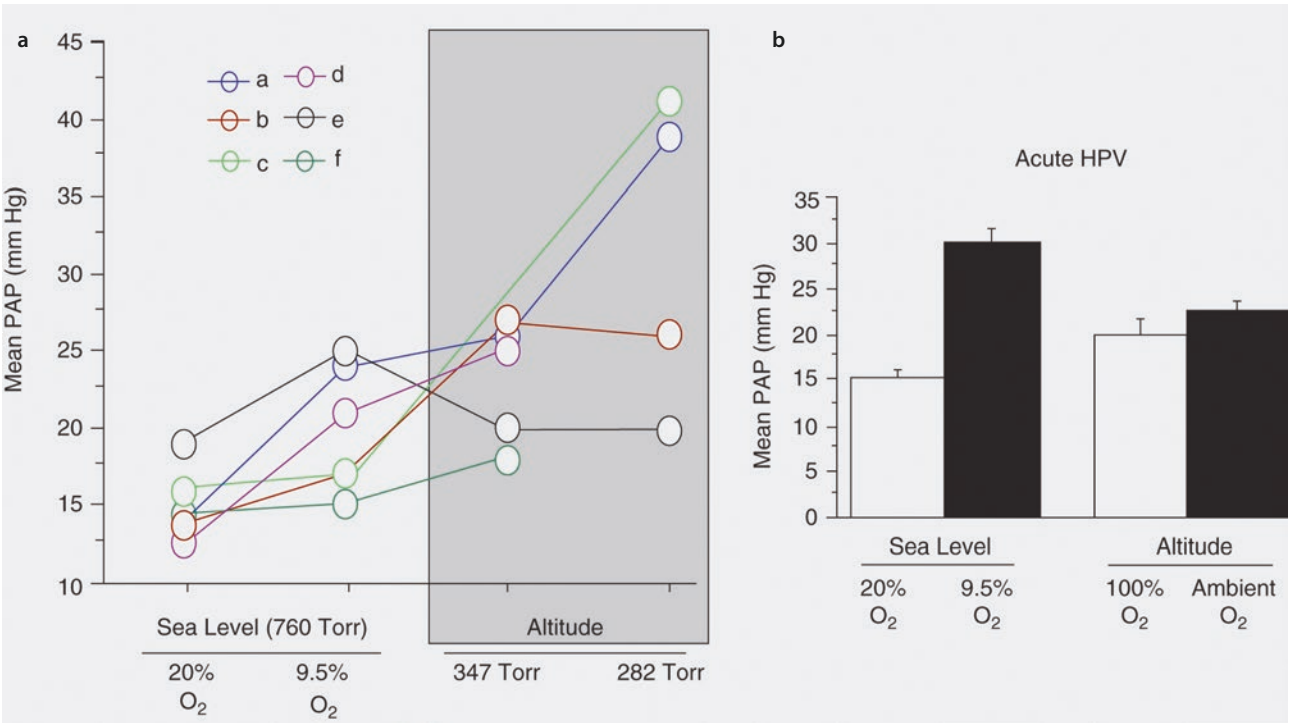
Although this response may optimize ventilation-perfusion matching when ventilation inequalities exist among different areas of the respiratory system, in some circumstances, this response can harm the patient. For example, at high altitude when barometric pressure and thus the partial pressure of inspired oxygen are low, the generalized alveolar hypoxia increases pulmonary vascular resistance and pulmonary artery pressure, which increases right ventricular workload and pressure. Similarly, in a patient who developed increased muscularization of their pulmonary arterioles with an elevated PVR (e.g., a postsurgical child who had a large right to left shunt), an obstruction in their endotracheal tube leads to a rapid fall in their P_AO_2 and thus an increased PVR that may lead to rapid clinical deterioration. With continued exposure to a hypoxic environment, the acute hypoxic pulmonary vasoconstriction response is diminished (◘ Fig. 15.5).

Hypoxic pulmonary vasoconstriction (HPV) is not a beneficial response in the presence of hypoxia affecting the whole lung (e.g., high altitude or endotracheal tube obstruction in a patient following surgical repair of a large right to left shunt).

The increase in pulmonary vascular resistance in response to decreased P_AO_2 is mainly caused by constriction of arterial vessels <500 μm. The effect of this vasoconstriction on the upstream, more compliant elastic vessels is an increase in their transmural pressure and thus their diameter. That is why measuring the right pulmonary artery diameter is used as a marker of pulmonary hypertension. Currently, it is generally accepted that all hypoxic vasoconstriction occurs upstream from the capillary bed and the site of fluid filtration.

Small arteries <500 μm are predominately responsible for hypoxic pulmonary vasoconstriction, and by distending the compliant elastic larger arteries, pulmonary hypertension may be recognized on the CXR.

Pulmonary vasoconstrictors such as catecholamines, histamine, prostaglandins, serotonin, and endothelin increase the potency of the hypoxic constricting response. Vasodilators such as bradykinin, adenosine, prostacyclin, and nitric oxide decrease the potency of the response.



◘ **Fig. 15.5** Dissociation of acute hypoxic pulmonary vasoconstriction from the hemodynamic response to chronic hypoxia. Volunteers in operation Everest were exposed to hypoxia in an altitude simulator. (**a**) The hemodynamic response to prolonged hypoxia in individual volunteers (a through f) was not predicted by their initial HPV response, suggesting a mechanistic dissociation between hypoxic pulmonary vasoconstriction and chronic hypoxic pulmonary hypertension. (**b**) Acute hypoxic pulmonary vasoconstriction is suppressed with chronic hypoxia (From Michelakis et al. (2004))

The larger the region of the lung that is hypoxic, the less pronounced is the blood flow diversion.

Hypercapnia augments and hypocapnia decreases the response to alveolar hypoxia. The larger the size of the hypoxic lung region, the less pronounced is the flow diversion. For example, if one lung is made hypoxic, about 50% of the blood flow to that lung is diverted, but when only 10% of the total lung is hypoxic, about 80% of the blood flow to that region is diverted. Animals that have adapted to high altitudes have no hypoxic pulmonary vasoconstrictive response. Finally, it is believed that there are genotypic and phenotypic differences among humans that account for why some are more prone to high altitude sickness and pulmonary edema than others.

15.8.5 Pulmonary Vascular Tone and Clinical Implications

The balance of circulating and local vasoconstricting and vasodilating factors is critical for the maintenance of the low basal pulmonary artery tone and resistance.

The pulmonary vascular bed is innervated and is continuously exposed to circulating vasoactive substances, which could affect PVR and blood flow. Maintenance of low PVR is of vital importance for humans, and there are multiple mechanisms to protect against the development of high pulmonary artery pressure.

15.8.6 Pulmonary Vasoconstrictors

G-protein-coupled receptors (Gs-vasodilation and Gq-vasoconstriction) are part of many pathways that control the basal vascular tone.

Most vasoconstrictor mediators have little effect in normal pulmonary vasculature, but they may cause or contribute to increased PVR in patients with preexisting pulmonary hypertension.

Multiple circulating vasoconstrictors have been identified (e.g., angiotensin II, ET-1, serotonin, norepinephrine, histamine, urotensin II, leukotrienes, and thromboxane), but they appear to have limited effect on normal PVR since the administration of specific receptor antagonists of these vasoconstrictors does *not* cause any further relaxation of the normal pulmonary circulation. These substances are believed to act on receptors that belong to the seven transmembrane families of G-protein-coupled receptors. Activation of these receptors activates phospholipase C leading to activation of protein kinase C, which through several steps increases intracellular Ca^+ concentration that results in smooth muscle contraction. Although these mediators are likely not important in patients with normal pulmonary vasculature, several of them have been implicated as a cause of pulmonary artery smooth muscle hypertrophy and vasoconstriction, and they may play a role in chronic pulmonary hypertension.

15.8.7 Pulmonary Vasodilators

Multiple endogenous substances (e.g., atrial and B-type natriuretic peptide, NO, prostacyclin, prostaglandin E_2, acetylcholine, bradykinin, epinephrine, substance P, vasoactive intestinal peptide) can dilate the pulmonary arteries and lower PVR when the muscular tone is increased either by a constrictor or by hypoxia. Studies using "knock-out" animals demonstrated that each one of these agents separately makes a minimal contribution to the maintenance of the low PVR.

Elevation of vascular smooth muscle intracellular cGMP or cAMP concentration causes vasodilation.

Pulmonary vasodilators act mainly through elevation of VSMC intracellular concentrations of cAMP or cGMP. Some agonists bind to G-protein-coupled receptors and through activation of adenylyl cyclase elevate the intracellular levels of cAMP. Atrial natriuretic factor has intrinsic G-cyclase properties. Bradykinin and acetylcholine bind to specific *endothelial* G-protein receptors and elevate intracellular Ca^+ which stimulates endothelial production of NO. If the endothelium is damaged, acetylcholine causes vasoconstriction by acting directly on muscarinic receptors on vascular smooth muscle.

Regulation of intracellular cAMP and cGMP concentrations is also influenced by the rate of their degradation, performed mainly by one of the phosphodiesterases (PDEs). Inhibition of the PDEs potentiates the effects of the vasodilators (e.g., milrinone and sildenafil for cAMP and cGMP, respectively).

15.8.8 Vasomediators in the Pathogenesis of Pulmonary Artery Hypertension (PAH)

An imbalance between endogenous vasoconstrictors and vasodilators may contribute to pulmonary hypertension.

In most patients with pulmonary hypertension, the resting vascular tone is increased. Vascular remodeling also is widely observed and consists of small artery smooth muscle thickening and extension of smooth muscle fibers into the nonmuscular small arterioles. There are likely multiple mechanisms resulting in PAH. For example, high blood flow and shear stimulates thromboxane production, which stimulates vascular smooth muscle growth. In other patients, increased endothelin is thought to lead to vasoconstriction and remodeling in pulmonary hypertension.

Many endogenous vasoconstrictors stimulate smooth muscle proliferation.

In patients with idiopathic pulmonary hypertension, urinary excretion of prostacyclin metabolites is decreased, but the excretion of thromboxane metabolites is comparable to normal controls. It also has been observed that endothelial nitric oxide synthase (eNOS) and PGI_2 synthase expression is reduced in resistance arteries of patients with pulmonary hypertension, suggesting that NO and PGI_2 production is decreased (Fig. 15.6). Additionally, increased expression of endothelin mRNA was observed in the small arteries of patients in the same population. Increased local expression of angiotensin-converting enzyme and circulating levels of ET-1 and serotonin were also documented in some idiopathic pulmonary hypertension patients. ET-1 acts on two receptors: ET_A and ET_B; both receptors on VSMC induce vasoconstriction, but ET_B on endothelial cells stimulates NO production. This has clinical implications since nonselective endothelin receptor antagonists are not as effective as selective ET_A antagonists in patients with pulmonary hypertension.

Many vasodilators also are antiproliferative agents.

Patients with pulmonary hypertension have increased circulating levels of ANP, BNP, and adrenomedullin, suggesting that there is an intrinsic effort to compensate via endogenous vasodilators and antiproliferative pathways. When the effects of the upregulated pathways of these factors can no longer compensate, vasoconstricting pathways dominate and severe pulmonary hypertension develops. Of note, monitoring the concentration of BNP may be useful to assess the severity and response to therapy in infants and children with PAH.

Selective ET_A receptor antagonists are preferred in the treatment of pulmonary artery hypertension.

Measuring BNP concentrations may be useful to monitor the response to therapy in children with PAH.

15.8.9 Autonomic Neural Regulation of Pulmonary Vascular Tone

Innervation of the pulmonary vascular bed by sympathetic and parasympathetic nerves is relatively sparse in comparison with that of the systemic circulation. There is relatively more innervation of the larger vessels and less of the smaller, more muscular vessels. There does not appear to be any autonomic innervation of vessels smaller than 30 μm in diameter, and there appears to be little innervation of the intrapulmonary veins and venules.

This autonomic innervation may have evolved to ensure that when the body is stressed by blood loss or some other major stress, increased autonomic activity will not elevate PVR to assure that the right ventricle can maintain cardiac output to the systemic circulation.

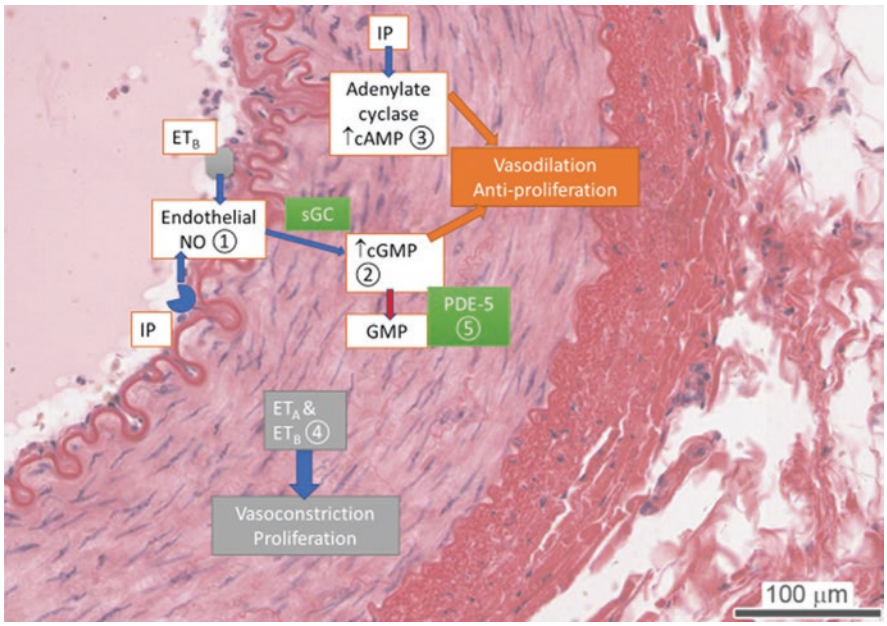


Fig. 15.6 Mechanisms associated with the treatment of pulmonary artery smooth muscle hypertrophy, proliferation, and vasoconstriction leading to pulmonary artery hypertension (PAH). ① Endothelial prostacyclin receptor (IP) and ET_B receptor stimulation increases endothelial production of nitric oxide (NO). The latter diffuses into VSMC cells, stimulating increased production of cGMP. Prostacyclin analogs are used to treat PAH and selective ET_A endothelin receptor antagonists are preferred in PAH treatment to avoid inhibiting the endothelial ET_B receptor. ② Increased intracellular cGMP concentration activates several pathways resulting in vasodilation and inhibiting muscle cell proliferation. ③ VSMC IP receptor stimulation activates adenylate cyclase, increasing intracellular cAMP concentration. Through several mechanisms, the latter produces vasodilation and inhibits smooth muscle proliferation. ④ VSMC endothelin receptor stimulation activates several pathways that produce vasoconstriction and stimulate smooth muscle proliferation. ET_A receptor inhibitors are beneficial in the treatment of PAH. ⑤ cGMP is degraded by phosphodiesterase type 5 (PDE-5) to GMP. Inhibiting PDE-5 activity in patients with PAH maintains higher intracellular cGMP concentrations and thus vasodilation. sGC is soluble guanylate cyclase

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The main sympathetic nerve effect is due to α_1-adrenoceptor-mediated vasoconstriction; when there is increased endogenous SNS activation, vasodilation results from β_2-adrenoceptor activation by circulating endogenous epinephrine or exogenous agonists.

The autonomic nervous system plays a modest role in the control of pulmonary vascular tone.

Cholinergic innervation causes mainly vasodilation, whereas sympathetic innervation causes predominantly vasoconstriction.

Neurogenic pulmonary edema in the presence of increased intracranial pressure or other brain injuries appears to result from a sudden increase in sympathetic activity that acutely results in volume and pressure overload of the pulmonary capillaries leading to pulmonary edema that can range from hydrostatic to hemorrhagic.

The vasoconstricting properties observed with sympathetic nerve stimulation are mainly due to α_1- and α_2-adrenoceptor activation. The effects are reduced by the α_1-adrenoceptor receptor antagonist prazosin. In this setting, vasodilation may be enhanced by activation of hormonal β_2-adrenoceptors by circulating epinephrine. Propranolol abolishes this vasodilation, whereas the β_2-adrenoceptor agonist albuterol relaxes pulmonary (and systemic) vascular tone and can at least partly overcome hypoxic pulmonary vasoconstriction; the latter action leads to increased intrapulmonary shunting and lower pulse oximetry saturations sometimes observed with albuterol use in patients with acute asthma.

Parasympathetic blockade does not alter the resting vascular tone, and therefore it appears that it does not play a crucial role in the maintenance of basal vasomotor tone. Vagal nerve stimulation has mixed effects because the vagus nerve carries both parasympathetic and sympathetic fibers. Intravenous administration of acetylcholine causes vasoconstriction at low vasomotor tone but vasodilation when the basal tone is elevated. Those responses are blocked by atropine, indicating that the action is secondary to muscarinic receptor activation. Studies in humans, rabbits, and guinea pigs showed that muscarinic M3 receptors located on endothelial cells mediate the vasodilatory response to acetylcholine by activating endothelial NO production.

Pulmonary edema secondary to catastrophic neurologic events is termed neurogenic pulmonary edema. It is thought that high intracranial pressure or other brain injuries (especially intracranial hemorrhage) are responsible for a reflex hyper-sympathetic state with sympathetic nerve overactivity and marked adrenal release of catecholamines. The marked increase in cardiac output combined with increased pulmonary vasoconstriction and increased tone in the

capacitance venous system shifts blood volume into the intrapulmonary circulation leading to acute elevation of pulmonary capillary hydrostatic pressure leading to acute hydrostatic pulmonary edema. In some patients, the high capillary pressures disrupt capillaries leading to hemorrhagic pulmonary edema.

15.9 Renal Circulation

The kidneys play a vital role not only in the maintenance of electrolytic balance and intravascular volume but also in the regulation of blood pressure. The latter is achieved by controlling water and sodium homeostasis and contributing to humoral control of systemic arterial tone through the renin-angiotensin-aldosterone system (RAAS). The importance of the kidneys is underscored by the fact that despite constituting only ~0.5% of human body mass, they receive about 20% of the cardiac output. On a weight basis, renal blood flow is more than four times greater than that of the heart. Since much of the high blood flow maintains the glomerular filtration rate (GFR) and is not needed for cellular oxygen delivery, oxygen extraction by the kidney is much lower than other organs, which is a major contributor to the higher venous oxygen saturation observed in the inferior compared with the superior vena cava.

The kidneys receive ~20% of the cardiac output, which is well in excess of its metabolic demand, to regulate water and sodium homeostasis and blood pressure through the RAAS.

Since much of the renal blood flow is to support GFR and not for oxygen delivery, renal vein oxygen saturation is normally elevated.

15.9.1 Major Arteries

The two major renal arteries (right and left) divide into the anterior and posterior main branches prior to their entry into the renal parenchyma. The anterior branch gives rise to four segmental arteries and supplies most of the anterior-apical surface and the lower pole. The posterior branch supplies the remainder of the kidney. Many branching variations exist with the most common being a separate renal artery originating from the aorta and perfusing the lower pole. A consequence of the renal arterial flow distribution is that the segmental arteries are terminal arteries that do not form collaterals or anastomoses with each other. Thus, an obstruction in one of the segmental arteries results in infarction.

Segmental arteries divide into smaller arteries. Blood from the arcuate arteries that course over the pyramids between the medulla and the cortex then enters perpendicular arteries that course from the arcuate arteries and branch into numerous arterioles, each of which enters a glomerulus as the afferent arteriole. After blood exits the glomerulus through a single efferent arteriole, most subdivide into a second set of capillaries, called the peritubular capillaries. These capillaries are widely distributed throughout the cortex in close proximity to the tubular segments. The peritubular capillaries then rejoin to form venules that drain into the renal venous system that exits the kidneys.

The renal segmental arteries are terminal arteries and do not form anastomoses. Obstruction in the segmental arteries results in infarction.

Arterioles at the border of the medulla and cortex give rise to deep penetrating bundles of arterioles, which are called vasa recta. The vasa recta provide the arterioles that surround Henle's loops and collecting ducts. They also supply blood flow to the inner medulla. After they reach the inner medulla, they reform the ascending vasa recta on their way back to the cortex.

Each glomerulus has an afferent and efferent arteriole.

The vasa recta, which are derived from the juxtaglomerular efferent arterioles, initially contain a smooth muscle layer which they lose as they penetrate deeper into the medulla where they evolve into capillaries. The ascending vasa recta have characteristic fenestrated endothelium. This histological change

Efferent arterioles at the border of the medulla and cortex give rise to deep penetrating bundles of arterioles which are called the vasa recta.

The ascending vasa recta have characteristic fenestrated endothelium that plays an important role in water and solute exchange in the medulla helping to maintain the osmotic gradient.

underscores the role of the vasa recta in not only providing nutrients and oxygen but also participating in water and solute exchange between the ascending and descending limbs of the vasa recta in the medulla, which helps maintain the osmotic gradient.

Blood that is relatively hemoconcentrated exits the glomerulus via the efferent arterioles at each nephron and continues into the peritubular capillaries and then subsequently into the venous system. Blood from the efferent arteriole provides nutrients to the distal portion of the proximal tubule, the loop of Henle, and the distal tubule. The corticomedullary junction glomeruli are responsible for modulating blood flow into the medulla. It is estimated that only 5–15% of total renal blood flow (RBF) is directed to the medulla with the outer medulla having higher blood flow (130–340 mL/100 g tissue/min) than the inner medulla (22–69 mL/100 g/min).

Only ~5–15% of the total renal blood flow enters into the medulla.

Approximately 15–20% of the plasma entering the kidneys is filtered into Bowman's space, which is the plasma filtration fraction.

Renal plasma flow is the amount of plasma flowing into the glomeruli. Clinically, renal plasma flow is difficult to measure directly and instead is estimated from renal blood flow and the hematocrit. If the cardiac output is 3.0 L/min/m^2 and 20% of this output flows to the kidney, then the renal blood flow is ~600 mL/min/m^2. With a hematocrit of 40%, the plasma component is thus 60%, so the renal plasma flow is ~360 mL/min/m^2. Approximately 15–20% of renal plasma is filtered in the glomerulus (i.e., glomerular filtration rate (GFR)), which is ~54–72 mL/min/m^2; the percentage of the plasma filtered is the plasma *filtration fraction* (Fig. 15.7). In an adult, this filtration generates 180 L/day, most of which is reabsorbed.

15.9.2 Renal Blood Flow and Autoregulation

Blood flow is regulated by the perfusion pressure difference between the arterial and venous vascular beds and the resistance of the arteries, arterioles, and capillaries. RBF regulation is unique since there are two sets of arterioles (afferent and efferent) and two sets of capillaries (glomerular and tubular). The main renal arteries and proximal arteries play a minimal role in resistance to flow. Most renal vascular resistance is determined by the afferent and efferent arterioles; under normal conditions, resistance is evenly distributed between the two.

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Because the afferent and efferent arterioles are arranged in series, their resistances are additive; thus, when they both contract, the total RBF will significantly decrease. Should the resistances within the afferent and efferent arterioles change in opposite directions, the net effect on total RBF is small; the effect on GFR depends on the change in hydrostatic pressure within the glomerular capillaries since they are positioned between the two arterioles. The independent adjustment of afferent and efferent vascular resistance allows for regulation of the glomerular capillary bed pressure over a wide range of systemic arterial pressures, which helps maintain a relatively constant GFR.

Regulation of renal vascular resistance is complicated by having two sets of arterioles (afferent and efferent with their own autoregulation and regulation by various mediators) and two sets of capillaries (glomerular and tubular).

The typical glomerular capillary hydraulic pressure is 60 mm Hg. The Bowman's space pressure is 18 mm Hg and the capillary oncotic pressure is ~29 mm Hg so the net glomerular filtration pressure is ~13 mm Hg.

The typical glomerular hydraulic pressure in adults is about 60 mm Hg. In contrast, the pressure within Bowman's space and the proximal tubules is approximately 18 mm Hg, and the capillary oncotic pressure is ~29 mm Hg. The net filtration pressure is capillary hydrostatic pressure - (Bowman's space pressure + capillary oncotic pressure), which gives a filtration pressure gradient of ~13 mm Hg. Since the glomerular capillary pressure is about 60 mm Hg and the peritubular capillary pressure is approximately 18–20 mm Hg, the perfusion pressure through the proximal nephron is ~40–42 mm Hg (Fig. 15.8). A detailed discussion on the formation and regulation of glomerular filtrate is beyond the scope of this chapter and is only discussed with respect to the effect it has on renal oxygen demand.

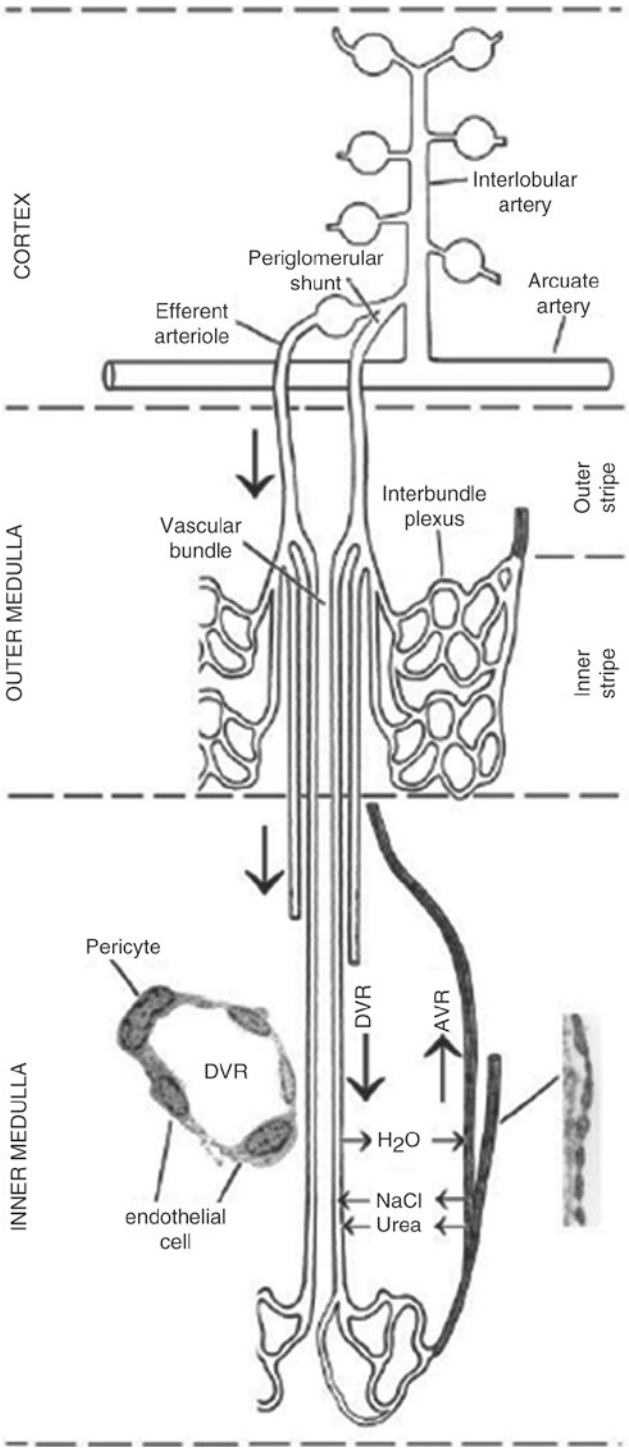

Fig. 15.7 Anatomy of the medullary microcirculation. In the cortex, interlobular arteries arise from the arcuate artery and ascend toward the cortical surface. Juxtamedullary glomeruli arise at a perpendicular angle from the interlobular artery. Most of the blood flow reaches the medulla through juxtamedullary efferent arterioles; however, some may also be from periglomerular shunt pathways. In the outer medulla, juxtamedullary efferent arterioles in the outer stripe give rise to descending vasa recta (DVR) that coalesce to form vascular bundles in the inner stripe. DVR on the periphery of vascular bundles give rise to the interbundle capillary plexus that perfuses nephrons (thick ascending limb, collecting duct, long looped thin descending limbs; not shown). DVR in the center continue across the inner-outer medullary junction to perfuse the inner medulla. Thin descending limbs of short looped nephrons may also associate with the vascular bundles in a manner that is species dependent (not shown). Inner medulla: vascular bundles disappear in the inner medulla, and vasa recta become dispersed with nephron segments. Ascending vasa recta (AVR) that arise from the sparse capillary plexus of the inner medulla return to the cortex by passing through outer medullary vascular bundles. DVR have a continuous endothelium (*inset*) and are surrounded by contractile pericytes. The number of pericytes decreases with depth in the medulla. AVR are highly fenestrated vessels (*inset*). As blood flows toward the papillary tip, NaCl and urea diffuse into DVR and out of AVR. Transmural gradients of NaCl and urea extract water across the DVR wall across aquaporin-1 water channels (Pallone et al. 2003)

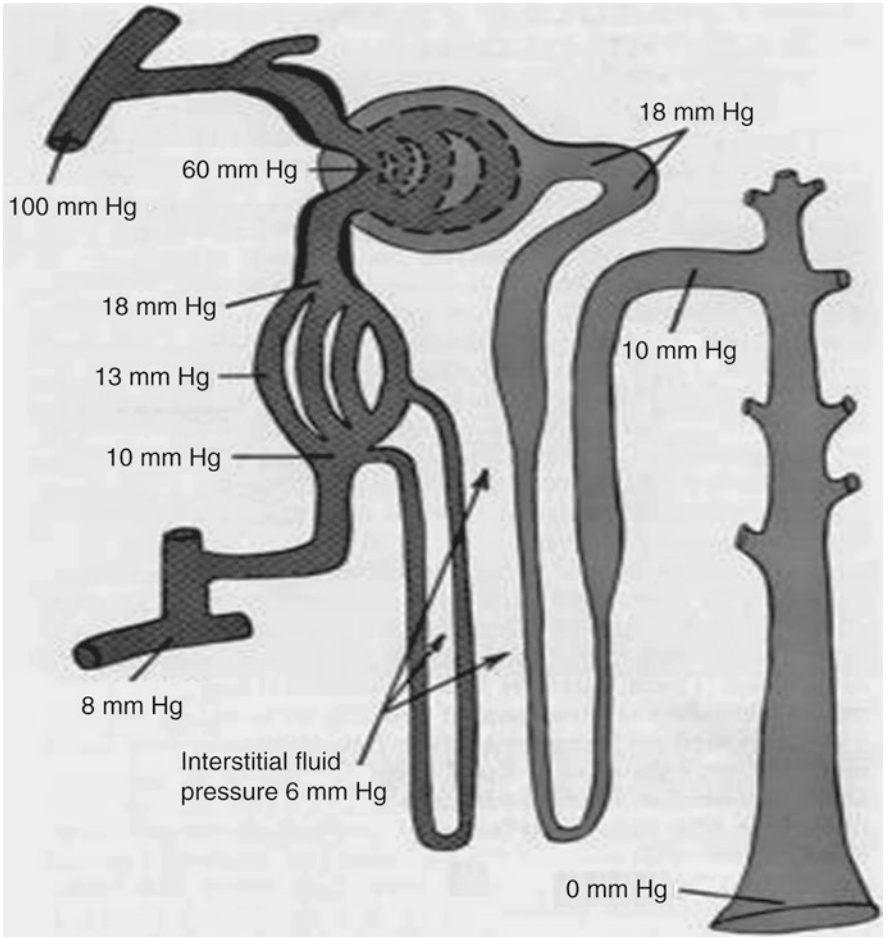

Fig. 15.8 Hydrostatic pressures in different parts of the kidney. Notice the perfusion pressure of the Bowman's capsule's arterioles is about 40–42 mm Hg (60–18 = 42 mm Hg). This figure does not illustrate the influence of the capillary oncotic pressure, which counteracts the capillary hydrostatic pressure

The kidneys regulate blood flow over a wide range of blood pressures to maintain relatively stable GFR. Within a range of normal mean arterial pressures of 60–180 mm Hg in adults, there is only a slight increase of GFR as pressures increase. Once the upper autoregulatory range is reached, further increases in blood pressure result in a steep increase in GFR. When the MAP falls below 60 mm Hg, the GFR declines significantly down to zero as the MAP falls. There are normal fluctuations in blood pressure throughout the day. To avoid exaggerated changes in GFR as a result of these variations in blood pressure, the kidneys employ two basic mechanisms to adjust vascular resistance: (1) the myogenic reflex and (2) tubuloglomerular feedback. When the renal perfusion pressure rises, the transmural pressure in the afferent arterioles stretches them leading to constriction (myogenic reflex). This mechanism is very fast (200–300 msec) and helps protect the glomerular capillaries that already experience a higher pressure than other systemic capillaries. Conversely, when perfusion pressure falls, afferent arteriole tone rapidly falls.

The tubuloglomerular reflex is a slower mechanism that adjusts afferent vascular resistance as well as sodium reabsorption. When the perfusion pressure increases, the myogenic reflex does not restore capillary hydrostatic pressure to normal, so the volume of filtrate increases, which delivers more sodium

and chloride to the distal tubule. The macula densa is located at the point where the nephron passes between the afferent and efferent arterioles. Increased sodium chloride delivery to the macula densa results in a vasoconstrictive response in the afferent arteriole that reduces glomerular filtration. Specifically, an increased uptake of chloride ions by the macula densa leads to ATP release into the surrounding extracellular space, which is then converted into adenosine and diffuses to bind to A_1 adenosine receptors on the afferent arterioles. Conversely, low sodium chloride delivery to the macula densa inhibits adenosine release leading to afferent arteriolar relaxation. Note that in the afferent arteriole, adenosine acts as a vasoconstrictor rather than a vasodilator.

To limit exaggerated changes in GFR, the kidneys respond to changes in systemic blood pressure with almost proportional changes in vascular resistance mediated by the myogenic reflex and tubuloglomerular feedback.

15.9.3 Medullary Blood Flow and Oxygen Demand

To achieve its complex function, the kidney needs an adequate supply of oxygen to maintain oxygen-dependent ATP production. The largest proportion of renal oxygen consumption occurs from activity of the Na/K-ATPase in the proximal renal tubule and medullary thick ascending loop of Henle. The reason for the high energy requirement is easy to understand when considering the implications of the filtration fraction. Roughly 20% of renal plasma flow is filtered at the glomerulus (i.e., ~140 mL/min or ~200 L/day in an adult). The plasma sodium concentration is ~140 mM, so the average adult filters 28 mol of sodium each day, equivalent to ~1.6 kg of NaCl. With a normal sodium intake of ~8 g/day, the kidney must reabsorb 99.5% of this filtered sodium load to stay in balance.

Within a range of normal mean arterial pressures of 60–180 mm Hg in adults, there is only a slight increase of GFR as pressures increase. Once the upper autoregulatory range is reached, further increases in blood pressure result in a steep increase in GFR.

When the MAP falls below 60 mm Hg, the GFR declines significantly down to zero as MAP falls.

The tubuloglomerular reflex is a significant intrarenal mechanism of vascular tone regulation.

High NaCl sensed by the macula densa leads to afferent arteriolar constriction mediated by extracellular adenosine that acts at afferent arteriole A_1 receptors to decrease local GFR.

Low NaCl sensed by the macula densa inhibits afferent arteriole constriction leading to an increase in GFR.

Achieving this reabsorption requires a considerable amount of energy from ATP production, which in turn requires consistent oxygen delivery to the renal tubular cells. It is estimated that ~80% of renal oxygen consumption is to fuel sodium chloride reabsorption in the kidney under normal physiologic conditions. This high level of renal tubular oxygen requirement explains why these cells are at increased risk of injury from tissue hypoxia.

In most organs, blood flow is determined by organ energy demand (metabolic activity). For example, skeletal muscle blood flow increases markedly when needed by exercising muscles. These actions are mediated by the local effects of NO, adenosine, and prostanoids. In contrast, increased renal blood flow often increases GFR, and the latter determines tissue oxygen requirements by increasing the sodium load to the tubules. Thus, rather than increasing blood flow to meet increased oxygen demand, preglomerular afferent arteriolar constriction reduces GFR which reduces Na delivery to the proximal and distal tubules, so less energy is required, producing a better match between oxygen delivery and demand.

It is likely that a differential response to renal tissue hypoxia developed to aid survival. For example, if blood volume needs to be conserved because of blood loss, reducing renal vascular resistance to preserve RBF in response to renal tissue hypoxia in this setting would result in more GFR and increased renal oxygen demand. Instead, the kidney needs to preserve intravascular volume *and* reduce GFR. The kidney has a diminished response to hypoxia, as observed in animal models ventilated with a hypoxic gas mixture; in this setting, blood flow increased to the brain and skeletal muscles, but not to the kidney.

Some tissues, like skeletal muscle, can use glycolysis and anaerobic metabolism for short-term energy production. The renal tubules, like neurons, require a continuous supply of oxygen to maintain their function (i.e., the tubule cells are obligate aerobic metabolizers). Interestingly, not only is the proximal tubule poor at glycolysis, but it is also actually a site for gluconeogenesis. Tubular cells in the thick ascending limb of the loop of Henle have the capacity for glycoly-

sis and thus can generate ATP in low oxygen environments. Even so, their sodium chloride transport activity can only be maintained by oxidative metabolism, and they are damaged in the absence of oxygen.

The kidney also appears to have limited capacity for angiogenesis. This may have evolved because the kidney is the "critometer" that responds to diminished oxygen delivery secondary to anemia (or hypoxemia in children with cyanotic heart disease) by increasing the production of erythropoietin, which is stimulated by hypoxia-inducible factor (HIF) in response to tissue hypoxia. To maintain that oxygen sensing function, the kidney cannot grow new blood vessels to increase tissue oxygen delivery. The price for this physiologic mechanism is increased renal susceptibility to capillary loss over time and thus increased risk of injury from tissue hypoxia.

15.9.4 Medullary Blood Flow

The high metabolic activity of the loop of Henle and the countercurrent flow of the descending and ascending vasa recta that are in close proximity allows oxygen to diffuse from the descending into the ascending vasa recta so that the PaO_2 in the deep medulla is only 10–15 mm Hg. This hypoxic environment explains why this region of the kidney is predisposed to injury when blood flow is decreased.

Although it was thought that medullary blood flow was heavily influenced by sympathetic nerve activation, more recent investigations revealed that medullary blood flow is minimally influenced by sympathetic nerve activation, especially when compared to the cortical renal blood flow. Medullary blood flow appears to be refractory to increases in circulating catecholamines within the physiological range. Only under extremely high concentrations of norepinephrine does medullary blood flow decrease. Two mechanisms are considered to be responsible for these unique physiologic property of the medulla: (i) the counterregulatory role of NO and (ii) paradoxical vasodilation in response to the effect of angiotensin II. It is thought that the different geometrical and environmental properties of the medulla are also responsible for the different response of medullary blood flow to sympathetic stimulation. Since the medulla is hypoxic at baseline, the medullary microenvironment is likely to produce mediators such as NO to preserve blood flow.

Medullary blood flow increases when metabolic activity increases. Acetylcholine, NO, kinins, adenosine, atrial peptides, and prostaglandins increase medullary blood flow. Angiotensin II (perhaps), vasopressin, endothelin, and extreme increases in renal sympathetic nerve activity can decrease medullary blood flow (Fig. 15.9).

Medullary blood flow seems to be refractory to increases in circulating catecholamines within the physiological range.

Two mechanisms are considered to be responsible for the unique blood flow characteristics of the medulla: (i) counterregulatory role of NO and (ii) paradoxical vasodilation in response to angiotensin II.

15.9.5 Cortical Blood Flow

Differences in regional blood flow within the kidney are well recognized; cortical blood flow declines from the outer to more inner layers. The outer cortical blood flow, calculated with various methods, is 500–600 mL/100 g/min, and the inner cortex has a blood flow of 200–300 mL/100 g/min. This mirrors the glomerular density gradient; there are more glomeruli in the outer than the inner cortex. During stress and hypotension, such as after significant hemorrhage, renal blood flow to the cortex is markedly restricted and is redirected to the medulla, which helps preserve oxygen delivery to meet the much higher metabolic activity in the medulla compared with the cortex. The mechanism for redirecting blood flow is possibly through a medullary bypass or shunt mechanism.

Outer cortical blood flow is double inner cortical flow.

During stress and hypotension, such as after significant hemorrhage, renal blood flow is redirected to the medulla possibly through a medullary bypass or shunt mechanism.

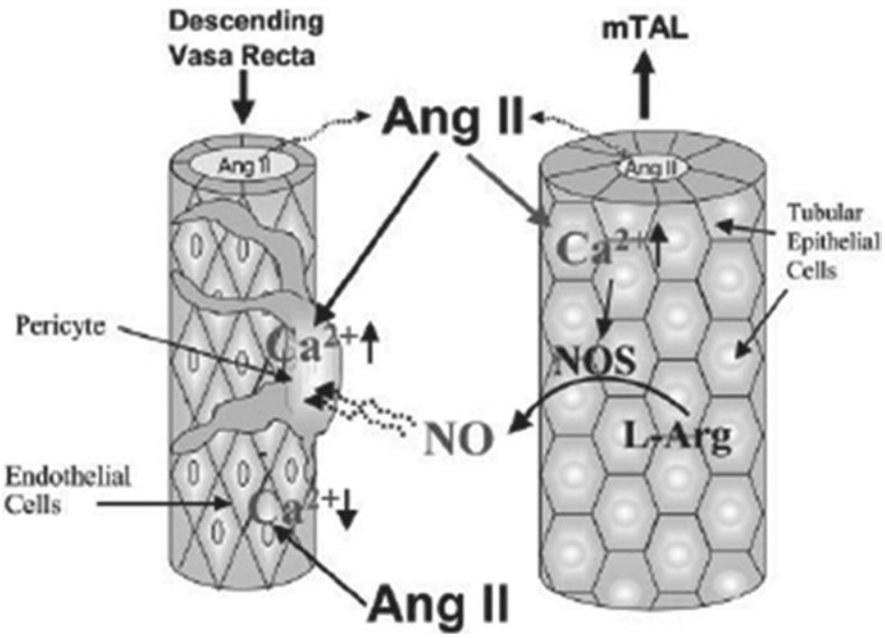

Fig. 15.9 Summary of the observed actions of ANG II on NO levels and intracellular Ca^{2+} concentration ($[Ca^{2+}]i$) in outer medullary vascular bundles. ANG II increases $[Ca^{2+}]i$ in pericytes of the descending vasa recta and reduces $[Ca^{2+}]i$ in the endothelium of the descending vasa recta. ANG II also increases [NO]i in the pericytes of the descending vasa recta but only when these cells are in proximity to the medullary thick ascending limb (mTAL) surrounding the outer medullary vascular bundles. ANG II increases $[Ca^{2+}]i$ and [NO]i in the mTAL even when these tubules were studied in isolation. These observations indicate that ANG II exerts a constrictor effect on the descending vasa recta by direct action on pericytes and that this constrictor action is buffered by NO diffusing from mTALs to the pericytes of the descending vasa recta (From Dickhout et al. (2002))

15.9.6 Sympathetic Nervous System (SNS) and Renin-Angiotensin-Aldosterone System (RAAS) Effects on Renal Blood Flow

Both the afferent and efferent arterioles are richly innervated. SNS activation by baroreceptors in the carotid artery and aortic arch respond to a fall in blood pressure in the carotid artery and aortic arch responds to a fall in blood pressure by rapidly increasing SNS activity, which increases arteriole tone to redirect blood flow from the kidney. This is mediated by activation of α_1-adrenoceptors, which reduces RBF, and thus renal solute and water filtration preserving intravascular volume.

Other physiologic stimuli for increased SNS activity are exercise and hypoxemia; the latter is mediated by chemoreceptors located in the carotid arteries. Hypoxemia also stimulates increased production of intracellular hypoxia-inducible factor (HIF), which is likely more than one mediator that activates various gene products depending on the cell.

The RAAS is activated by the SNS and via tubuloglomerular feedback where increased levels of angiotensin II (AII) reduce RBF and GFR by vasoconstriction of afferent arterioles more than the efferent arterioles. Renin is an enzyme formed and stored in granular cells of the afferent arterioles of the juxtaglomerular apparatus. Decreased afferent blood pressure, increased renal SNS activity (through activation of ß-adrenergic receptors on the juxtaglomerular cells), and decreased Na^+ concentration in the distal convoluted tubule filtrate are considered triggers for the release of renin. Renin increases AII; the latter has direct vasoconstricting effects through receptors on VSMC. AII also stimulates SNS activity by action at presynaptic receptors on sympathetic nerves to increase norepinephrine release, and AII stimulates the synthesis and release of aldosterone.

Increased SNS and RAAS activity in response to a decrease in blood pressure increases afferent and efferent arteriolar tone, redirecting blood flow from the kidney and preserving intravascular volume by reducing glomerular filtration.

Renin is released from granular cells in the afferent arteriole in response to ß-adrenoceptor stimulation, usually in response to a fall in blood pressure and/or reduced Na^+ concentration in the distal convoluted tubule.

15.9.7 Vasoactive Mediators

As in other vascular beds, there are a host of mediators that can affect renal vascular tone; some of the mediators produce different responses in the kidney compared with other vascular beds (e.g., adenosine). The net effect of any one mediator is difficult to predict since there often are competing signals received by the VSMC based on the local milieu.

Dopamine, acetylcholine, prostaglandin E_1, and prostacyclin dilate the afferent arteriole in rabbit preparations; bradykinin, adenosine, and prostaglandins D_2 and F_2 do not. The efferent arteriole dilates in response to dopamine, acetylcholine, prostacyclin, bradykinin, and adenosine. Other prostaglandins have no effect. The importance of vasodilator prostaglandins on RBF is clinically recognized by the adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs), which can compromise renal function even in the absence of critical illness if used in excessive doses or for prolonged periods (e.g., ketorolac).

Angiotensin II and endothelin cause afferent arteriolar constriction via direct action on VSMC.

AII and endothelin cause afferent arteriolar constriction through VSMC receptors, but both mediators also act on vascular endothelium to modulate NO production and regulation. Similar to the ET_A and ET_B receptors for endothelin, the angiotensin I receptor (AT1) is responsible for the vasoconstrictive action of AII, whereas the action of AII at the AT2 receptor on endothelial cells causes a dose-dependent dilation of the afferent arteriole by stimulating endothelial release of NO. All three endothelins, ET_1, ET_2, and ET_3 are potent vasoconstrictors of the renal vasculature through action at ET_A receptors on VSMC. ET_B receptors are also located on endothelial cells; stimulation of these receptors increases NO production. Of note, the ratio of ET_A:ET_B receptors in the medulla is 30:70, which is higher than in the cortex and may help maintain blood flow in the medulla when circulating endothelin is increased.

Both AII and endothelin also act through specific endothelial receptors (AT2 and ET_B) to increase NO production and release.

Nitric Oxide: Nitric oxide exerts tonic control on the afferent but *not* the efferent arterioles of the renal *cortex*. However, NO dilates both the afferent and efferent arterioles of the *juxtamedullary* nephrons. These different physiologic actions result from a distinctive physiological difference between the efferent arterioles of the cortex and medulla. Inhibiting NO synthase (NOS) enhances angiotensin II-induced afferent arteriolar constriction, suggesting that NO modulates the vasoconstrictor effects of angiotensin II on arterioles when angiotensin II levels are elevated. In the medulla, NO production serves an important counterregulatory role to blunt vasoconstrictor hormone-induced reduction of medullary blood flow and medullary tissue oxygen levels. When NOS activity is reduced within the renal medulla, sensitivity to vasoconstrictors increases dramatically and hypertension develops. Thus, renal medullary NO production plays a very important role in sodium and water homeostasis and the long-term control of arterial pressure.

Prostaglandins are important mediators of renal blood flow; use of potent or high-dose nonsteroidal anti-inflammatory agents can adversely affect RBF and renal function.

Nitric oxide exerts tonic control on afferent but not efferent arterioles of the cortex.

Nitric oxide dilates both the afferent and efferent arterioles of the juxtamedullary nephrons.

Medullary NO production serves as an important counterregulatory mediator to blunt vasoconstrictor hormone-induced reduction of medullary blood flow and tissue oxygen levels.

15.9.8 Adenosine and Renal Circulation

Adenosine is a breakdown product of ATP that has vasodilator properties in most vascular beds. Adenosine contributes to the microcirculatory metabolic control of organ perfusion, matching oxygen demand to delivery. However, as noted in the discussion on tubuloglomerular feedback, adenosine vasoconstricts the afferent arteriole when increased NaCl delivery is sensed by the macula densa. This action is mediated by A_1 adenosine receptors (A_1AR), which on afferent arterioles are selectively activated on the *interstitial* aspect of the vessel away from the vessels' interface with circulating blood. This property

dissociates A_1AR activation from changes in vascular adenosine concentration, a characteristic that is ideally suited for the role of renal adenosine as a paracrine factor in the control of glomerular function.

The initial renal vasoconstriction elicited by an intravenous infusion of adenosine is short lasting and is quickly followed within 1–2 min by vasodilation. It appears that the steady-state response to an adenosine infusion is global renal vasorelaxation due to action at A_2AR receptors on endothelial cells in most parts of the renal vasculature. The A_2AR-mediated vasorelaxation is probably facilitated by the endothelial location of these receptors, which cause the release of NO and other endothelial relaxing factors. Isolated perfused afferent arterioles, especially in their most distal segment at the entrance to the glomerulus, respond to adenosine with persistent vasoconstriction, indicating predominant or exclusive expression of A_1AR at this location to mediate the signal from the macula densa.

There are two adenosine receptors: A_1AR and A_2AR. Adenosine causes vasoconstriction in the afferent arterioles via activation of A_1AR located on the *interstitial* aspect of the afferent arteriole in close proximity to the juxtaglomerular apparatus.

Adenosine release from the macula densa mediates the tubuloglomerular feedback mechanism to reduce NaCl delivery to the macula densa by vasoconstricting the local nephron's afferent arteriole.

Efferent arteriolar vasodilation is caused by activation of A_2AR located on the vascular endothelium resulting in the release of NO and other vasodilator mediators.

15.10 Splanchnic Circulation

The splanchnic circulation regulates the blood flow to the gastrointestinal organs. Macro- and microvascular circulation is crucial to the functions of the gastrointestinal system, which includes digestion and absorption of nutrients as well as prevention of systemic infiltration from bacteria and antigens.

15.10.1 Vascular Anatomy and Distribution

Three different arterial branches originating from the aorta supply almost the entire gastrointestinal system: the celiac, the superior mesenteric (SMA), and the inferior mesenteric (IMA) arteries. The celiac artery supplies the stomach, upper duodenum, liver, spleen, and pancreas; the SMA, being the largest branch off the abdominal aorta, supplies the entire small intestine, proximal colon, and pancreas; the IMA delivers blood flow to the remainder of the colon down to the proximal rectum. Splanchnic blood flow is about 20% of the total cardiac output and is characterized by extensive collateral arteriolar overlap that helps ensure adequate perfusion. Approximately 30% of the circulating blood volume under normal conditions is located within the splanchnic circulation; ~70–75% of this volume is in the postcapillary venous system. Resting intestinal blood flow per gram weight is about 10 times higher than skeletal muscle (◘ Table 15.1) reflecting the higher baseline metabolic activity in the splanchnic circulation. Blood flow to the intestine and stomach increases substantially during a meal and returns to baseline levels as the chyme passes the specific region. The blood flow increase is independent of the hollow organ stretch and is primarily dependent on the chyme constituents.

Venous drainage from the intestines enters the portal venous system. Thus, the perfusion pressure for much of the splanchnic circulation equals the MAP minus portal venous pressure rather than the CVP. Perfusion to the GI tract may be impacted by cirrhosis and other factors that raise portal venous pressure. In addition, increased intra-abdominal pressure may compromise intestinal perfusion by reducing the perfusion pressure.

In the hollow organs of the gastrointestinal tract, the mucosal layer receives ~75% of the blood flow. All the other layers receive the remainder of the blood flow with the submucosal layer receiving less than 5%. Mucosal blood flow is primarily directed to the end loop arterioles of the villi and secondarily supplies the intestinal crypts and goblet cells. Similar to the renal medulla, there is

Three arterial branches supply the gastrointestinal system: the celiac, the superior mesenteric, and the inferior mesenteric arteries.

The basal splanchnic blood flow is ~20% of cardiac output.

Approximately 30% of circulating blood volume is located in the splanchnic circulation; most of the blood is in the postcapillary venous system.

a countercurrent blood flow exchange system perfusing the numerous intestinal villi responsible for nutrient absorption. The arteriole and venule are in close proximity so that oxygen can diffuse from the arteriole into the venule; thus, the distal villi have a relatively low tissue pO_2, which explains why the villi are the most sensitive portion of the splanchnic organs to reduced oxygen delivery.

During a meal, splanchnic blood flow increases up to 250% and returns to normal 2–3 h later.

Splanchnic blood flow during a meal increases up to 250% and is sustained at that level for up to 2–3 h before returning to baseline. This significant increase in blood flow is accomplished through arteriolar recruitment and vasodilation, but the control mechanisms are currently unclear.

The intestinal villi are perfused with a countercurrent blood supply, which creates low tissue oxygen tension in the distal intestinal villi and makes this tissue more sensitive to reduced splanchnic perfusion.

15.10.2 Baseline Vascular Tone Regulation

The principal vascular tone regulator of the large arteries and conduit vessels of the splanchnic circulation is the autonomic nervous system (sympathetic and parasympathetic). Increased parasympathetic activity increases intestinal motility and secretions, which indirectly increases blood flow secondary to increased metabolic demand. Various humoral agents that are commonly activated in critical illness or injury also play an important role in regulating splanchnic flow. At the microcirculation level, blood flow is predominantly controlled by the balance between a host of paracrine and metabolic mediators (◘ Table 15.4). Blood flow to the three layers of the intestine (mucosa, submucosa, and muscular) is regulated by metabolic demands and byproducts of metabolism such as pO_2, pH, PCO_2, and/or adenosine.

Large arterial tone is regulated primarily by the sympathetic nervous system; parasympathetic effects on the intestinal smooth muscle and glands increase metabolic demand, which secondarily increases blood flow.

Large arteries are under the direct tonic control of the vasomotor center of the central nervous system. Within larger arteries (>50 μm), the α-adrenergic tonic effect is more potent than the β-adrenergic effect resulting in a baseline vasoconstricted state. Intestinal blood flow autoregulation can sustain oxygen delivery over a wide range of perfusion pressures (MAP – portal venous pressure) between 40 and 120 mm Hg in adults.

Baseline vascular tone in the larger arteries is maintained by a predominance of α-adrenergic stimulation.

Autoregulation of intestinal blood flow sustains oxygen delivery over a wide range of perfusion pressures between 40 and 120 mm Hg in adults.

15.10.3 Postprandial Blood Flow Regulation

Blood flow to the intestinal and gastric mucosa can increase ~2.5-fold during a meal. Important triggers for the postprandial hyperemia are thought to be different nutrients and bile salts. During the anticipation and ingestion phases of a meal, the sympathetic nervous system increases blood pressure, heart rate, and cardiac output. In addition, it increases splanchnic vascular resistance. During the digestion and absorption stages and as the stomach fills with food, blood flow is increased to the stomach and duodenum in response to the chyme. Increased blood flow is specific to the segment that is in contact with the nutrients and lasts for as long as the flow of nutrients is sustained. Blood flow in each segment decreases as soon as the nutrients have passed through. During digestion, muscle and skin blood flow decreases while cardiac output and splanchnic flow increase.

Postprandial hyperemia is thought to be triggered by different nutrients and bile salts.

The hydrolytic products of food, especially glucose and the combination of fatty acids with bile salts, are responsible for the greatest increase in blood flow and hyperemia. How these nutrients control the increase of splanchnic blood flow is still not clear. There are five proposed mechanisms for postprandial hyperemia: (1) direct effects of absorbed nutrients, (2) enteric nervous system interactions and reflexes, (3) hormones and peptides, (4) local non-metabolic vasoactive mediators, and (5) local metabolic mediators. All these mechanisms

Hyperemia is regional; the increase in blood flow is sustained in the region as long as the flow of nutrients is sustained.

Table 15.4 Vasoactive mediators of the enteric circulation

Vasoconstrictors	Vasodilators
Neural mediators	
↑ Sympathetic tone (adrenergic)	↓ Sympathetic tone
Neuropeptide Y, peptide YY	↑ Parasympathetic tone (indirect effect)
Calcitonin gene-related peptide (CGRPa)	Vasoactive intestinal polypeptide (VIP)
Circulating humoral mediators	
Epinephrine (except in liver and muscle)	Epinephrine (only in liver and muscle) and dopamine
Angiotensin II	Histamine
Vasopressin	Bradykinin
Serotonin	Activated complement (C3a, C5a)
Activated complement (C5a)	Adrenomedullin
Paracrine and autocrine mediators	
Endothelin-1 (vascular smooth muscle cells)	Endothelium-derived relaxing factor (NO)
Platelet-activating factor	Endothelium-derived hyperpolarizing factor (EDHF)
Constrictor prostaglandins (e.g., F2α)	Dilator prostaglandins (e.g., prostacyclin)
Angiotensin II	Cholecystokinin and substance P
Metabolic vasodilators	
↑ pO_2	↓ pO_2
↓ PCO_2	↑ PCO_2
↑ pH	↓ pH
↓ Metabolites (K^+, lactate, adenosine, etc.)	↑ Metabolites

are designed to increase oxygen delivery to meet increased oxygen demand. For example, absorption of nutrients requires oxygen to generate the ATP needed; lipid micelle transport requires the largest oxygen consumption. In addition, the osmolarity of villus lymph and interstitial fluid increases from ~400 mOsm during the resting state to more than 600 mOsm during the absorption state. It is now believed that oxygen and osmolarity-dependent metabolic mechanisms play a crucial role in the initiation and maintenance of splanchnic hyperemia.

Direct effects of absorbed nutrients: Some nutrients act as direct vasodilators of the intestinal microcirculation after entering the bloodstream. For example, bile salts and micellar solutions can cause direct arteriolar dilation when injected intra-arterially. Some amino acids, as well as luminal carbon dioxide, when diffused across the epithelial mucosal barrier, can initiate vasodilation of the microvessels.

Enteric nervous system and reflexes: Sympathetic and parasympathetic innervation is not necessary for postprandial hyperemia, which implicates non-adrenergic and non-cholinergic neurons in the regulation of postprandial

There are five proposed mechanisms that control postprandial hyperemia: (1) direct effects of absorbed nutrients, (2) enteric nervous system interactions and reflexes, (3) hormones and peptides, (4) local non-metabolic vasoactive mediators, and (5) local metabolic mediators. All these mechanisms are designed to increase oxygen delivery to meet increased oxygen demand.

Oxygen and osmolarity-dependent metabolic mechanisms play a crucial role for the initiation and maintenance of splanchnic hyperemia.

Bile salts, amino acids, and a micellar solution can cause direct microvascular vasodilation.

Sympathetic and parasympathetic innervation does not contribute significantly to postprandial hyperemia.

Unidentified neurons have a regulating role in postprandial hyperemia.

Histamine, bradykinin, and serotonin are potent vasodilators in the intestinal microcirculation.

Partial pressure of oxygen, H^+ concentration, adenosine, and nitric oxide all contribute to local hyperemic regulation.

hyperemia. In addition, capsaicin and lidocaine can prevent micelle-induced jejunal hyperemia, suggesting that capsaicin-sensitive afferent fibers may also be involved.

Hormones and peptides: Many vasoactive hormones and peptides have been identified in the gastrointestinal system (gastrin, vasoactive intestinal peptide (VIP), cholecystokinin (CCK), substance P, secretin, gastric inhibitory polypeptide, neurotensin, calcitonin gene-related peptide, glucagon, enkephalins, somatostatin, and peptide YY), but they do *not* appear to have a role in postprandial hyperemia of the whole organ at physiologic concentrations.

Local non-metabolic mediators: Although the release of serotonin, histamine, bradykinin, and prostaglandins occurs in response to a wide range of physiological and pathological conditions, their role in regulation and control of intestinal hyperemia is unclear. Histamine, bradykinin, and serotonin are potent vasodilators in the intestinal microcirculation; histamine blockade of H_1 but not H_2 receptors diminishes the hyperemic response in the jejunum.

Local metabolic mediators: Increased oxygen demand, consumption, and debt in the villi stimulate active hyperemia. Reversal of hyperemia is coincident with a return to normal metabolic activity resulting in restoration of the tissue partial pressure of oxygen. From these observations, it is logical that increased local oxygen uptake and reduced tissue partial pressure of oxygen are the initial mediators for hyperemia. Increased levels of hydrogen ions and adenosine also promote direct vasodilation of the splanchnic vascular bed. Adenosine concentrations in the portal circulation increase 3–10 min before the mucosal increase of oxygen uptake and blood flow. Nitric oxide is also thought to have a synergistic role in combination with adenosine for local hyperemic regulation.

15.10.4 Pathological States

During shock states, splanchnic vasoconstriction induced by high sympathetic tone leads to critically low intestinal mucosal blood flow.

Unlike tissues that have high capillary density and low oxygen extraction at baseline, such as skeletal muscle that can recruit capillaries when metabolic demand increases, organs such as the intestinal tract are unable to recruit additional capillaries to maintain oxygen delivery. Conversely, much of the oxygen demand in the intestinal tract is mediated by active absorption of nutrients, which can be suspended during stress. Thus, during cardiogenic, septic, or hemorrhagic shock, perfusion of the intestinal mucosa may be reduced to 10% of basal blood flow due to SNS-mediated vasoconstriction of the large arteries and the arterioles at the level of the villi. Contraction of the venous system shifts blood volume back to the heart to support perfusion of the heart and brain. When blood flow to the mucosa is decreased substantially, the epithelial/mucosal barrier breaks down which contributes to a poor clinical outcome despite resuscitation and restoration of adequate blood pressure and cardiac output. This is thought to be due to the translocation of endotoxin and/or bacteria from the intestinal lumen, which activates an inflammatory response.

With resuscitation from intestinal ischemia, ischemic-reperfusion injury amplifies the initial injury. This injury is thought to be mediated initially by reactive oxygen metabolites followed by activation of polymorphonuclear neutrophils. Injury to the intestinal mucosa was thought to disrupt the normal gut-barrier function allowing endotoxin and bacteria to enter the portal circulation, but studies in animals and limited clinical studies do not consistently find endotoxin in the portal circulation. More recently, experimental data suggest that altered gut permeability leads to the delivery of pro-inflammatory

mediators via the mesenteric lymphatics, which drain into the thoracic duct, bypassing the liver, and instead are more likely to injure the lungs.

Increasing metabolic demand from enteral nutrition should theoretically worsen the mismatch between blood flow and oxygen demand during critical illness and may steal blood flow from other organs when cardiac output is low, but clinical studies found that providing enteral nutrition appears to protect the intestine from extreme vasoconstriction, even when the patient is receiving vasopressor infusions. This protective effect may be because enteral nutrition provides needed energy substrates for the intestinal epithelium. Conversely, total parenteral nutrition "starves" the intestinal epithelium and is associated with an increase in intestinal permeability following an ischemic-reperfusion injury; the latter is associated with higher mortality when compared with patients receiving enteral nutrition in different shock states. Intraluminal glutamine also was shown to be more protective to the mucosa during reperfusion injury than alanine.

Ischemic-reperfusion injury following resuscitation from shock is thought to be mediated by reactive oxygen metabolites followed by activation of polymorphonuclear neutrophils.

Intraluminal nutrients increase blood flow to the intestinal wall, which protects these cells from extreme vasoconstriction; this is at least partly by providing needed substrate to the intestinal epithelium.

Total parenteral nutrition cannot provide substrate to poorly perfused intestinal epithelium and is associated with an increase in intestinal permeability following ischemic-reperfusion injury. These effects lead to higher mortality when compared with enteral nutrition in different shock states.

Once reperfusion is achieved, enteral nutrition appears to limit further mucosal damage and reduces ischemic-reperfusion injury.

15.11 Cutaneous Circulation

The skin is the largest organ of the human body and serves as a barrier and thermoregulator. In addition, the skin provides environmental information processed by the brain to help regulate body temperature. The skin has significant blood flow (~5% of the total cardiac output at rest) that can be modified over a wide range for thermoregulation (◘ Table 15.1).

Thermoregulation is centrally controlled and adjusts blood flow to the skin. When the core temperature (Tc) is low or the temperature set point is increased, blood flow to the skin is reduced to limit radiant and conductive heat loss. Thus, as the temperature is *rising* in an infant or child, the skin will appear pale and cool to touch. If the core temperature is increased by increased muscle activity, or the temperature set point is reduced from an elevated level, such as after giving an antipyretic, skin perfusion increases markedly, and the patient appears flushed with warm skin to touch. These changes are mediated by neural and local mechanisms that directly influence the arterial tone and blood flow to the skin. With severe hyperemia, such as during heat shock, up to 60% of cardiac output is directed to the skin.

Regulation of cutaneous blood flow is a critical component of body temperature regulation mechanisms.

The arterioles of the glabrous areas of the skin (i.e., palms, lips, and soles of feet) are innervated only by sympathetic nerves, which are the primary regulators of blood flow. In the rest of the skin, blood flow is regulated by the balance between sympathetic and cholinergic parasympathetic nerves in addition to the effects of local skin temperature.

The balance between the sympathetic and parasympathetic nervous systems is critical for the regulation of nonglabrous skin blood flow.

During normothermia and resting conditions, there is no sympathetic stimulation so that the arteriole smooth muscles are at their basal tone. When heat loss is needed, neuronal regulation increases skin blood flow. If the skin temperature is increased along with the core temperature due to high ambient temperatures (as during heat stress), there is complete withdrawal of sympathetic tone on the arterioles. After complete suppression of sympathetic activity, sweating occurs, and if the core temperature continues to rise, parasympathetic vasodilatory tone increases leading to active maximal hyperemia.

When core temperature increases, cutaneous vasodilation occurs first by suppression of sympathetic baseline vasoconstriction, followed later by active parasympathetic-mediated vasodilation if the core temperature does not decrease toward baseline.

15.11.1 Cutaneous Vasodilation

Data suggests that stimulation of muscarinic cholinergic receptors is responsible for vasodilation mediated by parasympathetic activation. Data also sug-

The increase in blood flow due to active vasodilation in conjunction with sweating leads to heat dissipation and thermoregulation.

gests that cholinergic nerves release a co-neurotransmitter with acetylcholine; vasoactive intestinal peptide (VIP) has been implicated, but its role remains unclear.

Simultaneous release of acetylcholine and a co-mediator (VIP, NO) from parasympathetic neurons is thought to contribute to active hyperemia during heat stress.

Increased NO has also been associated with thermoregulatory vasodilation, and recent work showed that VIP-induced release of histamine from skin mast cells may lead to an increase in NO. Furthermore, acetylcholine mediates endothelial NO production early in the process. Excess NO production during sepsis has been implicated as a cause for "warm shock" characterized by excessive vasodilation with flushed skin. High local NO concentrations also blunt the vasoconstrictive response to agonist action at α-adrenoceptors.

Increased NO production is implicated in mediating the clinical picture of warm septic shock with cutaneous vasodilation.

15.11.2 Cutaneous Vasoconstriction

Vasoconstriction in the cutaneous arterioles is primarily controlled by α_1- and α_2-adrenoceptor stimulation through activation of sympathetic nerves and the action of circulating epinephrine, respectively. Vascular β_2-adrenoceptors are also stimulated by circulating epinephrine, and this action counteracts the effect of α-adrenoceptor stimulation. Thus, β_2-adrenoceptor blockade increases vasoconstriction even further. In addition, blockade of α- and β-adrenoceptors does not abolish cutaneous vasoconstriction due to cold exposure in humans. However, if complete prejunctional α- and β-adrenoceptor blockade is achieved, cold-induced vasoconstriction is abolished completely, suggesting that there is a co-transmitter released with norepinephrine. That co-transmitter is currently believed to be neuropeptide Y (NPY). Combined blockade of the NPY receptor and peripheral α- and β-adrenoceptors leads to total loss of vasoconstriction due to cold.

Although vasoconstriction is primarily thought to be secondary to α-adrenoceptor activation, blockade of β_2-adrenoceptors further increases vasoconstriction.

Neuropeptide Y, released with norepinephrine from sympathetic nerves, appears to contribute to cold-induced cutaneous vasoconstriction.

15.11.3 Local Temperature Control of Cutaneous Blood Flow

When the skin is heated, there is an independent mechanism of local arteriolar vasodilation that leads to increased skin blood flow proportional to the temperature increase with a maximum reached at 42 °C that lasts for 30–50 min. The initial pronounced vasodilation is followed by a plateau phase. Currently, it is thought that an unidentified local mediator is responsible for the vasodilatory response to local thermal stimulus.

Local warming of the skin leads to an increase of blood flow proportional to the increase in skin temperature up to 42 °C.

Local skin cooling significantly increases cutaneous arteriolar tone via sympathetic receptor activation and NPY activity pathways as described above. This local effect is independent of any core temperature changes. Local cold sensing nerves act as the afferent pathway that leads to norepinephrine and NPY release from sympathetic nerves. Continuous local cooling results in a non-neurally mediated continuous vasoconstriction; the mechanism for this effect is currently unknown.

Local skin cooling results in a significant increase of the cutaneous arteriolar tone via the activation of noradrenergic receptor activation and NPY excretion pathway.

Review Questions

1. Which of the following mediators has different effects on vascular tone in different vascular beds?
   A. Prostacyclin
   B. Bradykinin
   C. Endothelin
   D. Nitric oxide
   E. Oxygen

2. The right and left ventricles receive most of their blood flow during which phase of the cardiac cycle?
   A. Both during diastole
   B. Both during systole
   C. Left during diastole and right during systole
   D. Left during diastole and right continuously
   E. Left during systole and right during diastole

3. In which of the following conditions is the vasodilatory effect of elevated $PaCO_2$ in the cerebral circulation lost or blunted?
   A. Core body temperature of 32 °C
   B. Mean arterial pressure of 90 mm Hg with an intracranial pressure of 18 mm Hg
   C. Mean arterial pressure of 90 mm Hg with an intracranial pressure of 28 mm Hg
   D. Severe hypertension
   E. All of the above

4. What is the mechanism of hypoxic pulmonary vasoconstriction?
   A. A direct action on vascular smooth muscle
   B. Local release of a vasoconstrictor mediator
   C. Local suppression of a vasodilator mediator
   D. All of the above
   E. None of the above

5. Medullary blood flow of the kidneys appears to be refractory to increases in circulating catecholamines within the physiological range. Medullary blood flow decreases only with extremely high concentrations of norepinephrine. Which of the following mechanisms is responsible for this unique property?
   A. Counterregulatory role of nitric oxide
   B. Endothelin-induced vasodilation
   C. Paradoxical vasodilation as a response to the effect of angiotensin II
   D. Vasopressin-induced vasodilation
   E. A and C

6. In order to abolish human cutaneous vasoconstriction, what pharmacological blockade is necessary?
   A. Peripheral alpha and beta blockade
   B. Peripheral alpha blockade
   C. Peripheral beta blockade
   D. Peripheral alpha, beta, and neuropeptide Y blockade
   E. Peripheral neuropeptide Y blockade

7. Pulmonary vascular tone is regulated by a complex interplay of local mediators and neural regulation. Which mediator primarily causes pulmonary vasoconstriction?
   A. Acetylcholine
   B. Endothelin
   C. Bradykinin
   D. Natriuretic peptides
   E. Nitric oxide

8. Which is the most correct statement regarding regulation of splanchnic circulation?
   A. Increased local blood flow after a meal depends on the degree of hollow organ stretch.
   B. Hydrolytic products of food, especially glucose and fatty acids with bile salts, are triggers responsible for the greatest increase in blood flow in the prandial and postprandial states.
   C. The tone of larger splanchnic arteries is regulated by β-adrenergic effects more than the α-adrenergic effects resulting in a baseline vasodilated state.
   D. Sympathetic and parasympathetic innervation is primarily responsible for postprandial hyperemia.
   E. Vasoactive hormones and peptides have a significant role in postprandial hyperemia.

9. Which of the following is **NOT** a potential explanation for altered microcirculatory flow?
   A. Heterogeneity in microcirculatory perfusion
   B. Excess vasoconstriction mediated by increased adenosine concentrations
   C. Hemodilution, which reduces oxygen carrying capacity
   D. Vasoconstriction or tamponade of venous return
   E. Tissue edema increasing oxygen diffusion distance

10. Which of the following statements regarding splanchnic circulation is correct?
   A. Normal splanchnic perfusion pressure is the mean arterial pressure minus the intra-abdominal pressure.
   B. The most metabolically active tissue is the submucosa.
   C. Normal splanchnic perfusion pressure is the mean arterial pressure minus the portal venous pressure.
   D. Parasympathetic innervation of the vascular smooth muscle results in vasodilation.
   E. Most of the splanchnic blood volume is located in the arterioles and capillaries.

Answers

1. E
2. C
3. A
4. A
5. E
6. D
7. B
8. B
9. B
10. C

Suggested Readings

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Assessment of Cardiovascular Function

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Contents

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Learning Objectives

- Describe physical examination findings that aid in assessing the cardiovascular status of a critically ill child.
- Describe arterial pressure measurements and waveforms and how they are affected by various disease states.
- Describe central venous pressure measurements and waveforms and how they are affected by various disease states.
- Describe the utility of functional hemodynamics in the assessment of cardiovascular function.
- Describe the conservation of mass and Fick principles and how they relate to cardiac output measurement.
- Describe pulmonary artery pressure monitoring including estimation of cardiac output by thermodilution and measurement of pulmonary capillary wedge pressure.
- Identify the limitations of pulmonary artery catheterization.
- Describe pulse contour analysis tools used for the estimation of cardiac output in critically ill children.
- Identify and describe biochemical markers of cardiovascular function – specifically mixed venous and central venous oxygen saturations, lactate, B-type natriuretic peptide, and troponin measurements.

16.1 Noninvasive and Minimally Invasive Assessment of Cardiovascular Status

The physical examination remains the primary means to assess cardiovascular function. This includes evaluation of skin temperature, pulse rate and quality, capillary refill, and blood pressure. Altered mental status also may be associated with abnormal cardiovascular function.

With rapid access to portable bedside ultrasound and advances in noninvasive hemodynamic monitoring, the cardiovascular exam has been de-emphasized and physical examination skills among all levels of providers are at risk for deterioration. Despite inherent limitations, the physical examination remains the primary means by which intensivists assess cardiovascular function. Serial examinations are a readily available and inexpensive assessment tool that provides important physiologic data. In addition, the performance of serial examinations enables clinicians to build trust and rapport with children and families. An understanding of the clinical utility and limitations of examination findings is essential for the care of the critically ill child.

16.1.1 Physical Examination

A child with cardiovascular dysfunction can have important findings on general inspection. Cyanosis, a bluish discoloration of the skin and mucous membranes, may be either peripheral or central. Cyanosis is clinically recognized when *capillary* deoxygenated hemoglobin exceeds 5 g/dL; thus, a polycythemic patient with a hemoglobin of 16 g/dL experiencing a state of reduced peripheral perfusion may develop acrocyanosis with normal arterial oxygen saturation. Conversely, an anemic patient (e.g., a child with sickle cell disease and a hemoglobin of 6.5 g/dL) would not demonstrate capillary cyanosis even with an arterial oxygen saturation of 60%. Peripheral cyanosis is commonly due to cutaneous vasoconstriction secondary to exposure to cold or can be seen in low cardiac output states including hypovolemia, myocardial dysfunction, or septic shock. Central cyanosis is characterized by decreased arterial oxygen saturation (typically <85% assuming a normal hemoglobin concentration). Central cyanosis may be due to severe shock, venous admixture (e.g., cyanotic congenital heart disease), or dysfunctional hemoglobin (e.g., methemoglobinemia).

The jugular veins should be inspected. Presence of jugular venous distention (JVD) is a highly specific but not sensitive sign of elevated right atrial pressure (RAP). Distention is best assessed on the right side with the supine patient first lying flat and then with the head elevated 45°. Persistent distension at 45° and the absence of collapse during inspiration are suggestive of elevated RAP. Elevated RAP with restriction of right heart filling can occur with pericardial tamponade, tension pneumothorax, tricuspid valve stenosis, right heart failure, superior vena cava obstruction, or fluid overload.

JVD suggests elevated right atrial pressure, which may be secondary to restriction of right heart filling due to pericardial tamponade, tension pneumothorax, superior vena cava (SVC) obstruction, or tricuspid stenosis.

Tissue edema is most apparent in dependent regions including the lower extremities, sacrum, scrotum, and labia. Edema may be pitting when pressure is applied. Generalized edema is often due to disorders that produce low oncotic capillary pressure (e.g., nephrotic syndrome, malnutrition, liver disease) or those that increase capillary hydrostatic pressure (e.g., cardiac failure). Disorders such as sepsis and anaphylaxis may alter capillary permeability and also produce generalized edema.

Palpation of the pulse allows determination of rate, pulse quality, and skin temperature. Tachycardia is an early compensatory sign of cardiovascular compromise and is present in illnesses that decrease preload, increase afterload (e.g., catecholamine excess states), and decrease afterload (e.g., distributive shock) and conditions that compromise contractility (e.g., myocarditis).

Bradycardia often results from increased vagal tone but also may be due to sinus node dysfunction, atrioventricular block, drug toxicity, raised intracranial pressure, or hypoxemia. Abnormalities in the heart rhythm are a sensitive indicator of cardiac dysfunction. Rhythm alterations may be appreciated on palpation, but electrocardiography provides definitive evidence of an abnormal rhythm. Electrocardiography and continuous telemetry should occur in all children with suspected cardiovascular dysfunction.

Tachycardia or bradycardia alone is not a sensitive or specific indicator of compromised cardiovascular function. Fear, fever, dyspnea, and pain, all common in ill children, can also produce substantial tachycardia in the setting of normal or even high cardiac output states. Benign sinus bradycardia may be seen in the well-conditioned athlete or during deep sleep. Age-related differences may lead to the misinterpretation of high or low heart rates as abnormal by inexperienced examiners. The heart rate should always be assessed in the context of the patient's overall state (e.g., anxious, in pain, or sleeping) and not just compared to "normal" values for age.

Conditions that decrease the effective circulating volume such as dehydration, blood loss, excessive vasodilation, and capillary leakage of intravascular fluid can decrease preload and, subsequently, reduce cardiac output. Physical exam findings consistent with reduced preload include dry mucous membranes, sunken eyes, tachycardia, poor peripheral pulses, pulsus paradoxus, cool skin, delayed capillary refill, and ultimately hypotension.

Skin temperature and capillary refill can provide further assessments of tissue perfusion. Decreased cardiac output and a compensatory increase in systemic vascular resistance produce cool and poorly perfused extremities.

The peripheral skin temperature is usually measured as a toe temperature and normally is in the range of 32–34 °C. The ambient room temperature range is approximately 20–25 °C (68–77 °F). The delta peripheral-to-ambient (dTp-a) temperature gradient, also referred to as the toe-to-room temperature gradient, measures the difference in temperatures taken on the peripheral skin (toe) versus the ambient room temperature. The delta central-to-peripheral (dTc-p) temperature gradient measures the difference between skin temperatures obtained on the core (thorax) versus the periphery (toe). Both gradients have been studied as early markers of hemodynamic instability. With a stable ambient temperature, the dTp-a decreases and the dTc-p increases during states of high systemic vascular resistance. During vasoconstriction, the temperature of the skin falls, thus causing the dTp-a gradient to decrease. Heat conduction from the core decreases during vasoconstriction causing the central temperature to rise and the dTc-p gradient to increase.

Trending changes in skin temperature and gradient measurements are valuable adjuncts to the clinical assessment of microcirculatory integrity. Recent studies in patients with severe infections have supported the use of gradient changes, especially a decreasing peripheral-to-ambient (toe-to-room temperature) gradient, as a reflection of compromised microcirculation.

Since Beecher's original description in 1947, the assessment of capillary refill time (CRT) has been both revered and maligned in the medical literature. Like other bedside clinical observations, CRT can be affected by interobserver, environmental, and physiologic variables. Normal CRT after applying 5 seconds of pressure to the skin should be less than 2 seconds. CRT should be measured when the ambient temperature is between 20 and 25 °C.

Environmental factors such as low ambient temperature and poor lighting have been shown to decrease CRT utility. Cooler ambient temperatures produce prolonged CRT versus warmer temperatures. The anatomic site where CRT is assessed has important implications for its clinical utility. To properly assess CRT, the extremity should be above the level of the heart to avoid the influence of venous congestion. If CRT is assessed with the extremity lower than the level of the heart, CRT may reflect venous capillary refill as opposed to the desired arteriolar capillary refill. Severe anemia also makes assessment of CRT less reliable.

Prolonged CRT is a specific, but not sensitive, sign of low cardiac output states. Children with prolonged CRT have a greater risk of progressive shock than children with normal capillary refill time. However, its low sensitivity means that a normal CRT does not rule out cardiovascular dysfunction. Despite inherent limitations, CRT remains a useful clinical tool to serially assess cardiovascular function in the critically ill child.

Environmental factors (e.g., low ambient temperature and poor lighting), venous congestion, and anemia decrease the reliability of capillary refill time.

Although prolongation of CRT is often associated with compromised cardiac output, the examiner should also be aware of hyperbrisk or "flash" capillary refill. Disease states associated with low systemic vascular tone and normal or even increased cardiac output can produce rapid refill time. Flash capillary refill can be seen in certain forms of septic ("warm") and distributive shock.

Palpation of the liver is an important part of the cardiovascular exam. Hepatomegaly, edema, and jugular venous distention may be present in acute or chronic heart failure especially if the right heart is predominately affected.

Cardiac auscultation should occur over the tricuspid, pulmonary, mitral, and aortic areas with the bell and diaphragm of the stethoscope. The first heart sound (S1) is produced by mitral and tricuspid valve closure. S1 marks the end of diastole and the beginning of systole and is best heard over the lower left sternal border. The second heart sound (S2) is crisper and shorter than S1 and is produced by aortic and pulmonary valve closure. The physiologic splitting of the S2 into first aortic valve closure and subsequent pulmonic valve closure is best heard during inspiration over the upper left sternal border. Recall, inspiration increases right heart volume and will therefore slightly delay closure of the pulmonic valve.

Conditions that delay pulmonary valve closure can widen splitting and include right bundle branch block, pulmonary valve stenosis, and pulmonary hypertension. Right heart overload lesions may result in a widened and or fixed splitting of the S2. Fixed splitting occurs when S2 remains split in both inspiration and expiration. Conditions that produce large left to right shunts such as atrial septal defects and anomalous pulmonary venous connections into the right atrium can result in fixed splitting of S2.

Conditions such as right heart volume overload, pulmonary stenosis, pulmonary hypertension, and right bundle branch block result in a widened S2 split because pulmonary valve closure is delayed.

Careful auscultation can also identify new or changing murmurs, extra heart sounds (e.g., gallops), or abnormal sounds such as rubs, clicks, or muffled sounds. It is important to discern the timing (systole versus diastole) and the intensity of the abnormal sound.

16.1.1.1 Respiratory Signs

Although respiratory rate and work of breathing are considered respiratory signs, they can also be useful signs in children with suspected cardiovascular dysfunction. Quiet tachypnea (i.e., increased respiratory rate without an increase in the work of breathing) may be a sign of respiratory compensation for the presence of a perfusion-related metabolic acidosis. In an infant or child with signs of impaired perfusion, increased work of breathing may be due to increased pulmonary venous pressure and cardiogenic pulmonary edema.

16.1.1.2 Urine Output

Although not a true examination finding, urine output remains an important surrogate for end-organ perfusion. The kidney receives the second highest blood flow, relative to its mass, of any organ in the body. Urine output reflects the glomerular filtration rate, which in turn reflects renal blood flow; in the setting of shock, urine output reflects vital organ perfusion. The measurement of urine output serves as an excellent proxy to detect poor cardiac output from abnormalities in preload, afterload, and/or contractility. A normal urine output is approximately 1 mL/kg/h and should be a therapeutic target during resuscitation of hypovolemic, septic, and distributive shock.

Urine output should not be used as a proxy of organ perfusion when inappropriate diuresis occurs due to toxic ingestions (e.g., osmotic agents, diuretics), hyperosmolar states (e.g., diabetic ketoacidosis), diabetes insipidus, and cerebral salt wasting. A vigorous urine output in these cases may ultimately lead to intravascular volume depletion. Alternatively, children with inappropriate antidiuretic hormone release may have decreased urine output that may not be reflective of intravascular volume depletion but rather may be more consistent with volume overload.

16.1.2 Noninvasive Blood Pressure

A variety of physiologic factors contribute to the components of blood pressure.

16.1.2.1 Systolic Arterial Pressure

Systolic pressure is determined primarily by the force and volume of the blood ejected by the left ventricle (LV) and the compliance of the arteries the blood is ejected into. LV ejection results in distention of arterial walls and pulse waves that "bounce" back off the arterial walls. Both the pressure generated by ejection and reflected pulsatile waves off arterial walls contribute to the systolic pressure. Stiffer, less compliant arteries produce reflected waves that contribute far greater to the systolic pressure than do compliant arteries. Compliant arteries act to absorb rather than reflect pressure waves.

16.1.2.2 Diastolic Arterial Pressure

Diastolic pressure is determined by the time needed for systolic pressure to dissipate (pressure decay) and the resistance to volume displacement in the arterial tree (arterial distensibility). Blood flows more rapidly from the arterial system when the arteriolar resistance is low or when there is a connection to a low resistance system (e.g., a patent ductus arteriosus or large arteriovenous malformation)., Additionally, if there is incompetence of either the aortic or pulmonary valve, retrograde blood flow will cause a decrease in respective dia-

stolic pressures. In general, diastolic blood pressure correlates with the SVR; when SVR is low, the diastolic blood pressure will be low.

16.1.2.3 Pulse Pressure

Narrow pulse pressure is seen in aortic stenosis or low cardiac output states such as occurs with hemorrhage, tamponade, and cardiogenic shock. Widened pulse pressure is seen with PDA, systemic to pulmonary shunts, severe aortic regurgitation, and low SVR states such as distributive shock and vasodilated septic shock.

Systolic pressure minus the diastolic pressure equals the pulse pressure. Monitoring changes in pulse pressure can be clinically useful. Pulse pressure can be increased with conditions that raise stroke volume and thus systolic pressure, such as hyperadrenergic states (e.g., fever, pain, exogenous catecholamines, hyperthyroidism) and in states with increased arterial rigidity that increase the contribution of reflected waves to the systolic pressure (e.g., aging, arteriosclerosis).

Pulse pressure may also be increased in conditions that lower diastolic pressure due to abnormal runoff of blood into a lower resistance circuit as noted above or due to low systemic vascular resistance (SVR) states (e.g., warm sepsis, anaphylaxis, spinal shock, exogenous vasodilators). Patients with significant anemia (e.g., sickle cell disease) need a high cardiac output to maintain normal tissue oxygen delivery; thus, SVR is low in these patients who characteristically have a wide pulse pressure. In general, the normal diastolic blood pressure is approximately two-thirds of the systolic pressure; a wide pulse pressure may be clinically recognized by a diastolic blood pressure ≤ one-half the systolic blood pressure.

Narrowing pulse pressure due to falling stroke volume and systolic pressure with compensatory preservation in diastolic pressure is often a sign of worsening shock. Conversely, a diastolic blood pressure ≤ one-half the systolic blood pressure suggests a low SVR state such as seen in warm sepsis.

A narrowed pulse pressure can be seen in children with aortic stenosis or low cardiac output states. Hemorrhage, tamponade, and cardiogenic shock can cause progressive narrowing of pulse pressure. As stroke volume and systolic pressure decrease, compensatory mechanisms that increase SVR help preserve mean and diastolic pressure. Left unchecked, a rapidly narrowing pulse pressure can be an ominous sign.

16.1.2.4 Mean Arterial Pressure (MAP)

Physiologically, the MAP is determined by the force of blood ejected from the LV, vascular tone of the arterial system, and central venous pressure (CVP). This relationship is reflected in the formula:

$$\mathrm{MAP} = \left(\mathrm{CO} \times \mathrm{SVR}\right) + \mathrm{CVP}$$

CO (cardiac output) and SVR are often not readily quantifiable at the bedside. MAP can be approximated by utilizing the diastolic and pulse pressure:

$$\mathrm{MAP} \approx \text{Diastolic Pressure} + 1/3 * \text{Pulse Pressure}$$

MAP is not an absolute mean of diastolic and systolic pressures because the duration of diastole is longer than systole. As heart rate increases and systole shortens, the MAP approaches the true arithmetic mean of systolic and diastolic pressures.

Noninvasive methods of blood pressure determination include auscultatory and oscillometric methods. Auscultatory determination of blood pressure requires the identification of Korotkoff sounds as the extremity cuff pressure decreases. The initial sound is produced by turbulent flow in the artery and marks the systolic pressure. The disappearance of these sounds determines the diastolic pressure.

Oscillometric determination of blood pressure is accomplished by automated blood pressure devices such as the Dinamap (device for indirect noninvasive mean arterial pressure). As the cuff pressure declines and blood flows through arteries, the pressure in the cuff oscillates. The start of measurable oscillations marks systolic pressure, whereas the maximal level of arterial wall

oscillations marks MAP. The diastolic pressure is recorded at the point when the oscillations stabilize. It is commonly observed that the oscillometric method underestimates diastolic blood pressure since it is not directly measured and instead is estimated based on the algorithm used by the manufacturer.

Both auscultatory and oscillometric determination of blood pressure are limited by technical and physiologic factors. Inappropriate cuff size can lead to underestimating (cuff too large) or overestimating (cuff too small) true arterial pressure. An appropriate size cuff should have a bladder width at least 40% of arm circumference. The inflatable bladder length should cover 80% of the circumference of the arm. Noninvasive methods are less reliable in children with low cardiac output states, peripheral arterial disease, excessive extremity edema, subclavian artery abnormality (e.g., Blalock-Thomas-Taussig shunt), and during arrhythmias.

Too large cuff size can lead to underestimating blood pressure, and too small cuff size leads to overestimating blood pressure. If the distal pulse cannot be palpated, oscillometric blood pressure determination is unreliable.

16.1.3 Echocardiography

Over the last decade, use of focused cardiac ultrasound (FoCUS) to assess hemodynamics has increased dramatically in pediatric critical care. Bedside ultrasound allows the rapid assessment of pericardial disease, cardiac function, and functional hemodynamics such as fluid responsiveness. The ability to rapidly obtain high-quality images allows the intensivist to corroborate physical examination findings or alternatively, to appreciate hemodynamic changes that are not apparent on the examination.

The performance of echocardiography by non-cardiologists should occur after formal training and be limited in scope. FoCUS in critically ill children can often aid in the differentiation of shock (e.g., distributive, hypovolemic, obstructive, or cardiogenic) and allow targeted and prompt therapeutics.

16.1.3.1 Pericardial Disease

Pericardial effusions can be rapidly identified during FoCUS evaluation (◘ Fig. 16.1). The nature of the effusion (e.g., free flowing versus loculated) and its physiologic impact can be assessed. Tamponade physiology occurs when raised intrapericardial pressure overcomes chamber pressures and compromises cardiac filling. An echocardiographic feature of cardiac tamponade is collapse of the right atrium and the right ventricle. Chamber collapse occurs during atrial and ventricular relaxation phases, when intra chamber pressures are lower than pericardial pressures. Therefore, right atrial collapse usually occurs during systole and right ventricle collapse during diastole. Atrial collapse during systole often precedes diastolic ventricular collapse. Collapse of the left atrium is rarely observed, but its presence in conjunction with right atrial collapse increases the likelihood of cardiac tamponade. Dilation of the inferior vena cava due to high atrial pressures is an additional echocardiographic feature consistent with tamponade.

If drainage of a pericardial effusion is necessary, utilizing ultrasound to provide real-time guidance during pericardiocentesis or pericardial catheter placement greatly improves safety and success rates.

16.1.3.2 Systolic Function

Myocardial contractile function can be initially assessed in a nonquantitative manner. Experienced examiners can often quickly determine if a ventricular contraction appears to be robust or reduced. However, serial assessments, especially if done by multiple examiners, require objective measurements to

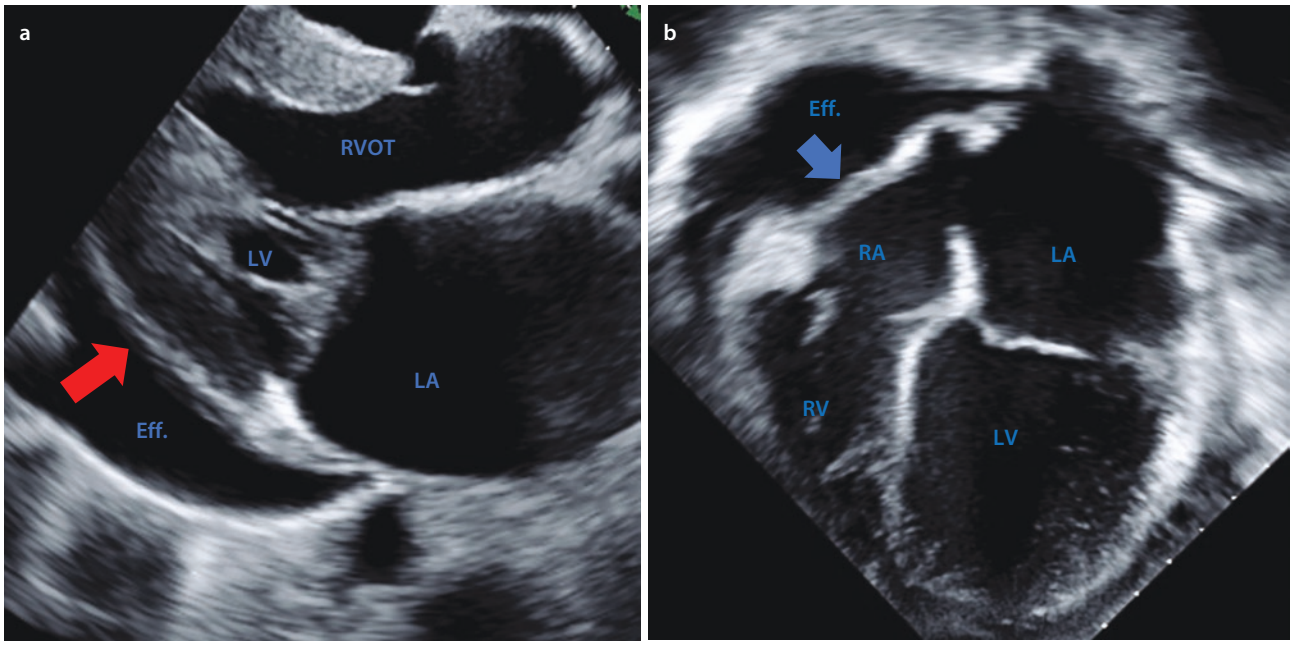

Fig. 16.1 **a** Moderate to large sized pericardial effusion (Eff.) present on FoCUS parasternal long-axis view. The effusion is increased along the left ventricular free wall (red arrow). **b** Right atrial collapse is noted (blue arrow)

describe systolic function. Ejection fraction (EF) and fractional shortening (FS) are common quantitative measurements obtained using FoCUS. It is important to appreciate that both EF and SF can be affected by aberrations in afterload and preload. If preload or afterload is not optimized, EF and SF will be abnormal and may not reflect intrinsic myocardial function.

EF utilizes the change in ventricular volume that occurs from systole to diastole to assess systolic function. Using the standard 2D mode, apical views are obtained. End-systolic and end-diastolic LV internal diameters are measured at the level of the mitral leaflet tips in the parasternal long-axis view. These measurements are then used to estimate the end-systolic and end-diastolic volumes (ESV, EDV), respectively. Using Simpson's method, EF is calculated using the equation:

$$\mathrm{EF}(\%) = \left[(\mathrm{EDV} - \mathrm{ESV})/\mathrm{EDV}\right] \times 100$$

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Ejection fraction utilizes the change in LV volume that occurs from systole to diastole (i.e., the SV) to assess systolic function, whereas fractional shortening utilizes changes in LV dimension that occurs at end-diastole and end-systole (LVEDD and LVESD).

EF is categorized as normal (≥55%), slightly reduced (41–55%), moderately reduced (31–40%), and markedly reduced (≤30%).

M-mode is used to estimate wall thickness and chamber dimensions and is obtained from parasternal or long-axis views. Left ventricular function can be estimated by measuring the left ventricular dimension in end-diastole and end-systole (LVEDD and LVESD). The fractional shortening (FS) is calculated using the following equation:

$$\mathrm{FS}(\%) = \left[(\mathrm{LVEDD} - \mathrm{LVESD})/\mathrm{LVEDD}\right] \times 100$$

Normal values for FS in infants and children are between 28% and 46%. The fractional shortening assumes that the ventricle has a symmetric cylindrical shape. Diseases with abnormally shaped ventricles (e.g., hypoplastic left ventricle) and those causing asymmetric wall abnormalities reduce the ability of FS to reflect overall systolic function.

16.1.3.3 Volume Status and Fluid Responsiveness

The evaluation of preload and the cardiac output response to fluid administration is difficult to predict in children. Central venous pressure (CVP) and pulmonary capillary wedge pressure have inherent limitations and require invasive catheter placement.

Left ventricular size can be assessed rapidly by FoCUS and has been utilized to assess preload. However, only extremes in size tend to provide clinical utility. A very small hyperdynamic LV suggests hypovolemia and fluid responsiveness.

FoCUS also utilizes the measurements of the maximal inferior vena cava (IVC) diameter, collapsibility index (the percentage decrease in IVC diameter with inspiration), and the IVC/aorta diameter ratio to assess preload. Adult studies found FoCUS assessment of preload and fluid responsiveness to be clinically useful. Multiple small pediatric studies evaluating the utility of FoCUS to determine volume status have yielded inconsistent data. FoCUS should be used with caution as a stand-alone measure of preload and fluid responsiveness in critically ill children.

16.1.3.4 Pulmonary Artery Systolic Pressure

Understanding the normal RV and LV relationship can aid in the diagnoses of pulmonary hypertension. The RV is thin walled and has an anterior triangular shape and crescent cross-sectional shape. When visualized in the short-axis and apical four-chamber views, the RV cavity area appears smaller than the LV with a normal RV to LV area ratio range between 0.65 and 0.90. An increase in this ratio occurs with acute elevation in PA pressures (RV distension) or with chronic pulmonary hypertension (RV dilation). Right ventricular area equal to LV area indicates mild dilation, while area ratios approaching 2:1 indicate severe dilation.

During a normal cardiac cycle, LV pressures exceed RV pressures and the ventricular septum can be seen bowing into the RV. Elevated right ventricular pressures cause the intraventricular septum to flatten or even bow into the LV cavity. This change in the normal position of the septum is best appreciated in the parasternal long- or short-axis view during diastole and systole and is a sensitive marker of right ventricular hypertension in children (◘ Fig. 16.2). On the short-axis view, the dilated RV causes flattening of the septum and the LV cavity takes on the appearance of the letter D.

Measuring the maximal tricuspid valve regurgitation (TRV, m/s) is used to estimate pulmonary artery systolic pressure. The pulmonary artery systolic pressure (PASP) is quantified using the modified Bernoulli equation:

$$\mathrm{PASP} = 4 \times \left(\mathrm{TRV\,max}\right)^2$$

The normal estimated pulmonary artery systolic pressure (PASP) is <30 mm Hg.

Adding the right atrial pressure, if known, to the PASP estimates the RV systolic pressure (RVSP):

$$\mathrm{RVSP} = 4 \times \left(\mathrm{TRV\,max}\right)^2 + \mathrm{RA\ pressure}$$

16.1.4 Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) technology is predicated on the physical properties defined by the Beer-Lambert law. The law states that there is a linear relationship between the absorbance of light passing through a solution and the concentration of an absorbing substance (known as chromophores).

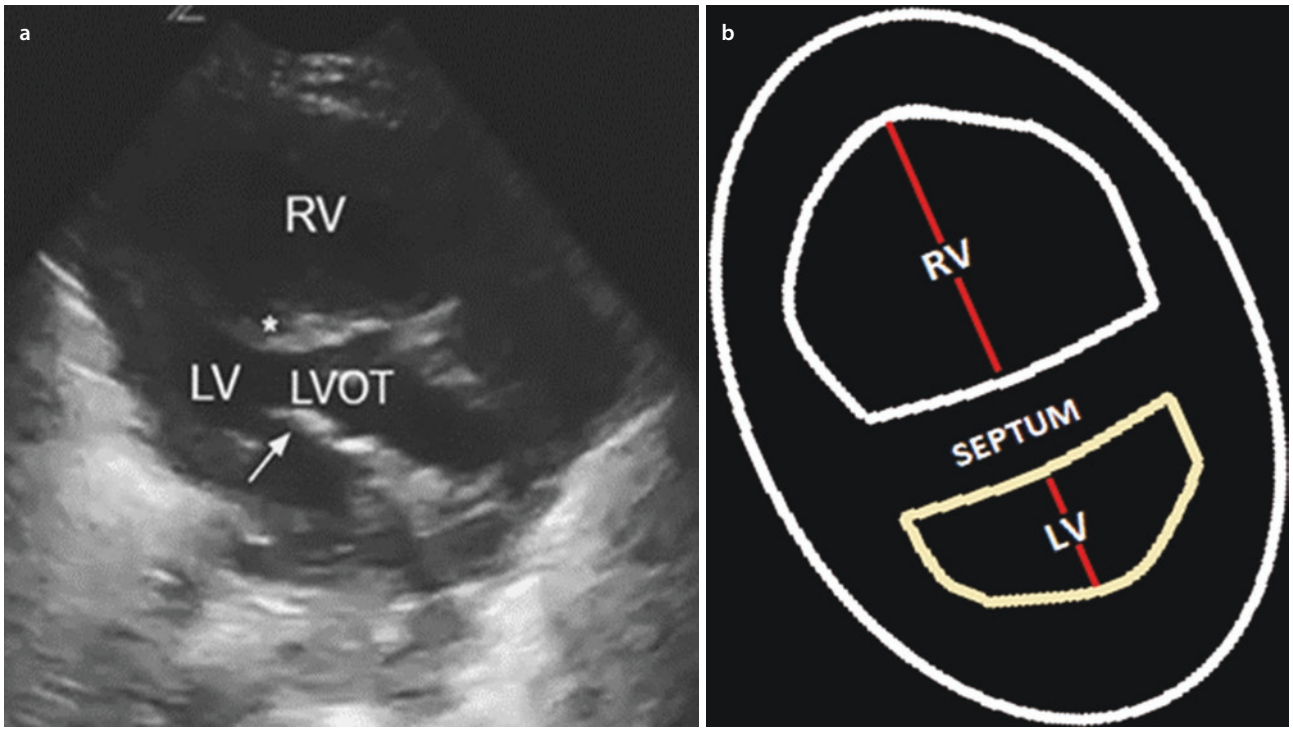

Fig. 16.2 **a** Parasternal view shows a severely dilated RV, septal bowing (asterisk). (Image courtesy of Dr. Shira Shore). **b** Graphic displaying D-sign seen in parasternal short-axis view. RV dilation causes septal flattening and D-shaped LV. The D-sign can be due to RV pressure overload (e.g., pulmonary embolism, pulmonary hypertension) or volume overload (e.g., tricuspid regurgitation, aggressive fluid resuscitation). D-sign seen during diastole and systole is likely due to pressure overload, whereas D-sign seen only in diastole is likely due to volume overload

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NIRS utilizes the different light absorptive qualities of oxygenated and deoxygenated hemoglobin to estimate oxygen saturations mainly in the venous compartment of tissue beds 2–3 cm below the skin surface. It does not require pulsatility and can be used to assess regional saturations of the cerebral, splanchnic, and renal microcirculations.

In applying NIRS technology to evaluate tissue perfusion, the solution that the light is transmitted through is blood in the arteriolar, capillary, and venule compartments. The main chromophores in the solution are oxygenated and deoxygenated hemoglobin (Hb). Each form of Hb has differential absorption of light in the near-infrared spectrum (700–1150 nm). Deoxygenated Hb is absorbed at 650–1000 nm and oxygenated Hb 700–1150 nm. Using a mathematic algorithm, NIRS can subtract the effects of weak chromophores (e.g., adipose tissue) to focus on the light absorption of Hb in the oxygenated and deoxygenated states.

The amount of blood in the arteriolar, capillary, and venular compartments exists in a ratio of 10:20:70%, respectively. Thus, the majority of the NIRS measurement occurs in the post-oxygen extraction venule compartment and reflects a value similar to a mixed venous oxygen saturation (SvO_2). Unlike pulse oximetry that is dependent upon pulsatility to determine arterial oxygen saturation, NIRS technology does not require pulsatility and may have greater utility during states of poor peripheral perfusion.

The NIRS measurement reflects the regional oxyhemoglobin saturation (rSO_2) in tissues 2–3 cm below the sensor. Light photons in the NIR spectrum are capable of penetrating dense structures such as the skull. Thus, cerebral NIRS penetrates the forehead to assess cerebral tissue perfusion in the frontal cortex.

Common sites for regional somatic measurements are the forearm, flank, or upper chest. NIRS-derived saturations are referred to as ScO_2 (cerebral), StO_2 (tissue), or rSO_2 (regional). StO_2 and rSO_2 have been used interchangeably. A NIRS sensor placed over a kidney or intestinal area may be referred to as renal StO_2 (Fig. 16.3) and splanchnic StO_2, respectively.

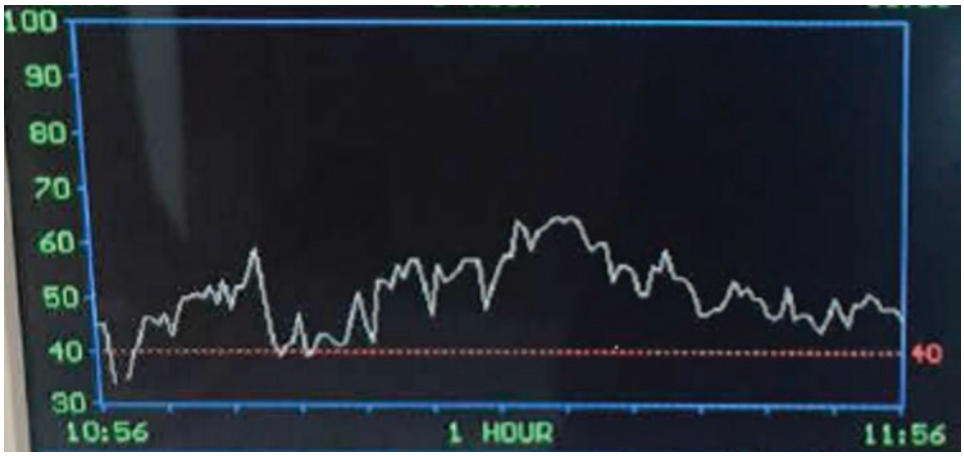


Fig. 16.3 Renal StO_2 displaying improved oxygen saturations after intervention. The subsequent decline is consistent with persistent circulatory dysfunction on examination. (Courtesy of Dr. Ravi Samraj)

Table 16.1 Summary of patient-related and technologic limitations of NIRS for the assessment of regional tissue perfusion

Patient-related limitations	Technologic limitations
Skin conditions: Burn Overlying infection Hyperpigmentation Overlying scar Excessive underlying adipose tissue	Regional saturations may not reflect global perfusion
Pigment conditions: Hyperbilirubinemia Excessive myoglobin	Lack of standardization across devices and lack of absolute values
Hemoglobin abnormalities: Polycythemia	Cost

NIRS has been used as a microcirculatory proxy for central venous oxygen saturation ($ScvO_2$) to assess the adequacy of oxygen delivery in critically ill infants and children. Populations in which NIRS has been utilized include children with shock, acute neurologic disease, and those postoperative from congenital heart disease (CHD) repair.

In infants postoperative from CHD repair, NIRS-derived saturations correlate with $ScvO_2$. Both cerebral and renal StO_2 of less than 65% correlate with postoperative hyperlactatemia (>3 mmol/L) in neonates postoperative from CHD repair. NIRS may have particular utility in the single ventricle population. Low regional cerebral oxygen saturation in the first 48 h after the Norwood procedure had a strong association with adverse outcome.

NIRS has both technologic and patient-related limitations that are summarized in Table 16.1. Cerebral NIRS values may not reflect the perfusion of less proximate brain tissue and other regional circulations. In addition, cerebral NIRS values that reflect clinically significant cerebral tissue desaturation remain undefined. Multiple studies have used different thresholds of ScO_2 for interventions ranging from 50% to 70%. Some authors have defined cerebral tissue desaturation as greater than a 20% reduction from baseline. Due to the lack of absolute values, most authors advocate for utilizing cerebral and somatic NIRS technology to monitor trends in perfusion. Cerebral NIRS in traumatic brain injury may be limited as cerebral edema or hematoma may affect the ability to accurately detect changes in perfusion in underlying tissue.

Due to multiple potential limitations, cerebral NIRS values must not be interpreted in isolation. Consideration of macrocirculatory oxygen delivery indicators (e.g., examination, functional hemodynamic measures, $ScvO_2$, lactate, pH) in conjunction with NIRS measurements will provide a more accurate assessment of the physiologic state of the child.

16.2 Invasive Measures of Cardiovascular Function

16.2.1 Arterial Waveform Analysis

Intravascular arterial catheters provide continuous monitoring of arterial pressure as well as important physiologic data derived from waveform analysis. The normal waveform begins with aortic valve opening and the onset of LV ejection (Fig. 16.4). This is seen as a sharp upstroke in the waveform referred to as the *anacrotic limb*. After its peak, aortic pressure declines as LV ejection slows. The descending limb is interrupted by a small rise in pressure. When arterial pressure is measured in the aorta, this rise in pressure produces a notch termed the *incisura* and is related to the elastic recoil of the aortic valve after its closure. When arterial pressure is measured peripherally, this rise in pressure is referred to as the *dicrotic notch.* During peripheral intra-arterial monitoring, the notch is not due to the recoil following aortic valve closure as is commonly thought, but rather, it is due to reflected waves back from distal arterial walls and branch sites. Diastolic runoff and end-diastolic pressure complete the waveform.

Several changes in the arterial pressure waveform occur as the pulse wave is transmitted distally. The systolic peak increases, the dicrotic notch occurs later, and the diastolic pressure becomes lower. Consequently, a larger pulse pressure is measured in distal arteries. Despite these changes, the MAP is only slightly

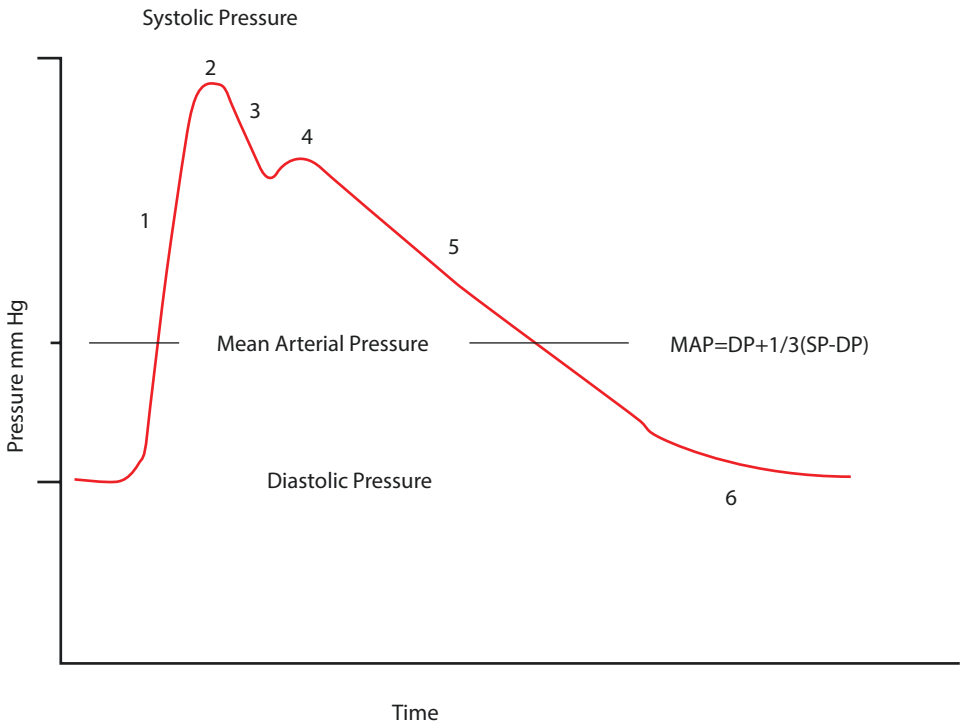


Fig. 16.4 Normal arterial waveform analysis: (*1*) sharp upstroke – *anacrotic limb*, (*2*) peak systolic pressure, (*3*) decline in aortic pressure as LV ejection slows, (*4*) notch in descending limb – *incisura* or *dicrotic notch*, (*5*) diastolic runoff, and (*6*) end-diastolic pressure

lower in the periphery than in the aorta. These changes are due to the phenomenon of *distal wave amplification*. Although blood flow rate from the aorta to the distal arteries falls only slightly, flow rate falls markedly at the arteriolar level. This is due to the significant increase in resistance encountered at the arteriolar level. The high resistance to flow diminishes pressure pulsations to the small downstream vessels, but also causes pressure pulsations to reflect back upstream. Therefore, the contour of a peripheral arterial waveform is determined by both forward pulsations originating from LV ejection (stroke volume) *and* reflected pulsatile waves from distal vessel walls and bifurcation points. Clinically, these reflected waves become more pronounced with stiff noncompliant arteries. In the elderly, systolic hypertension is due, in part, to a loss in the arterial distensibility causing reflected waves to add to the systolic peak.

16.2.1.1 Arterial Waveform Technical Considerations

Prior to ascribing an abnormal arterial waveform to a physiological perturbation, it is essential to rule out a mechanical artifact. To better understand the technical limitations of intra-arterial monitoring, a brief discussion regarding the technical principles that govern pressure waves is helpful.

Wave Frequency and Resonance

Invasive arterial monitoring systems consist of an intravascular catheter connected to low-compliance, saline-filled tubing that provides a continuous fluid column to an electronic transducer. The pressure waveform of the arterial pulse is transmitted via the column of fluid to the pressure transducer where it is converted into an electrical signal. These signals are then amplified, displayed, and recorded. The pressure waveform generated by a pulse is not a simple single sine wave that is transmitted through the fluid column. Instead, it is a combination of a *fundamental* wave (also referred to as the first harmonic wave) which corresponds to waves produced by LV ejection and a series of *harmonic* waves which correspond to waves produced by reverberations reflected back from the vascular tree. The fundamental frequency corresponds to pulse rate; by convention, a pulse of 60 beats per minute equals 1 Hz (cycle/s). Harmonic waves are smaller waves whose frequencies are multiples of the fundamental frequency and can occur at rates of 2, 3, 4 Hz, etc. Fourier's theory states that any complex waveform, such as an arterial pressure waveform, is constructed from the sum of all waveform frequencies (Fig. 16.5). Fourier analysis is the mathematical process of converting a complex waveform (with all its constituent sine waves) into a single pressure waveform.

The contour of a peripheral arterial waveform is determined by both forward pulsations originating from LV ejection and reflected waves from distal vessels and bifurcation points.

In an ideal environment, the summation wave produced by LV ejection and arterial reverberations would be the only wave the transducer would convert into an electrical signal. As in any complex system, however, the ideal is seldom realized. Instead, the arterial pressure wave causes the monitoring system to

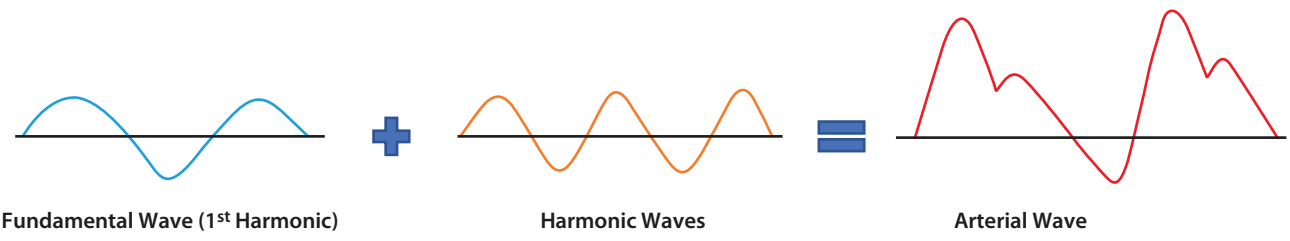


Fig. 16.5 The arterial waveform is made up of the sum of the fundamental sine wave and the harmonic waves. Although a simplified representation, the shape of the arterial waveform is due to the additive effects of the fundamental sine wave (pulse wave from ejection) and subsequent harmonic waves (pulse waves reflected off arterial walls)

oscillate freely and thus produce its own set of sine waves. The frequency of the oscillations is called the system's *natural frequency*. If the natural frequency of the system is in the same range as the natural frequency of the arterial waveform, the amplitudes of the waves become additive or *resonant*. Clinically, resonant augmentation of the arterial pressure wave causes an artifactual increase in systolic pressure and a decrease in diastolic pressure. Systolic pressures may be falsely increased by as much as 30%.

Resonant augmentation of the arterial pressure wave can cause an artifactual increase in systolic pressure and a decrease in diastolic pressure with systolic pressures falsely increased by as much as 30%.

Resonance becomes problematic when the monitoring system has a low natural frequency and the heart rate is high. Therefore, resonance amplification can occur when the natural frequency of the system approximates the frequency of the constituent sine waves that make up the arterial pulse. Accurate measurement of an arterial pressure is accomplished by assuring the natural frequency of the measurement system is at least eight times higher than the frequency of the arterial pressure wave, which is equal to the heart rate. Thus, an accurate monitoring system at heart rates of 120 bpm (i.e., 2 Hz) should have a natural frequency equal to or above 16 Hz. The desired frequency is obtained by first converting pulse rate to Hz and then multiplying by a factor of 8:

Accurate measurement of an arterial pressure is accomplished by assuring the natural frequency of the measurement system is at least eight times higher than the frequency of the arterial pressure wave.

$$(120\,\text{bpm} / 60\,\text{Hz}) \times 8 = 16\,\text{Hz}$$

Damping

In addition to the effects of the natural frequency of the monitoring system (potential for resonance), the system's own physical forces may interfere with accurate measurement of the arterial pressure. Damping describes the interaction between the oscillatory energy of a wave and the physical properties of the monitoring system. Damping causes a progressive diminution of a system's inherent oscillations. In an ideal system with no damping effects, the oscillations of a wave would continue indefinitely at the system's *undamped natural frequency*. However, in reality, wave oscillations are always affected by the physical forces of the monitoring system (i.e., friction, compliance, and elastance) so that the frequency of oscillations occurs at the system's *damped natural frequency*. A monitoring system is optimally damped if it dissipates the physical forces produced by its components and selectively conducts the oscillations of the pressure waveform. Optimal damping is difficult to achieve. Inadequately damped systems (*underdamping*) result in the system producing many sequentially decreasing reverberation waves that occur in response to each pulse wave. When the frequency of these reverberation waves (also referred to as ringing) approaches the arterial pulse wave frequency, resonance occurs, and systolic pressure is overestimated. An underdamped waveform is characterized by a high initial spike in the waveform. Underdamped systems may be due to excessive tubing length or vasoconstriction. Long tubing causing an underdamped system seems counterintuitive; if there is more tubing, then it seems logical that the tubing would absorb energy, causing overdamping. However, this is not the case. As the tubing length increases, the natural frequency of the system approaches the patient's pulse wave frequency. The system then resonates, amplifying the signal. Thus, excessive tubing length causes resonance in the system, and consequently the system will be underdamped.

Underdamping results in excessive resonance which in turn artificially increases systolic pressure.

A system is overdamped when the oscillatory energy of the pressure wave is reduced by the physical forces of the system. O*verdamping* results in an artificially low systolic blood pressure. Causes of overdamping include multiple stopcocks, leaks, bubbles, clots, compliant tubing, or kinks in the cannula or tubing (Fig. 16.6).

Overdamping causes the oscillatory energy of the pressure wave to be reduced by the system's physical forces and results in an artificially low systolic blood pressure.

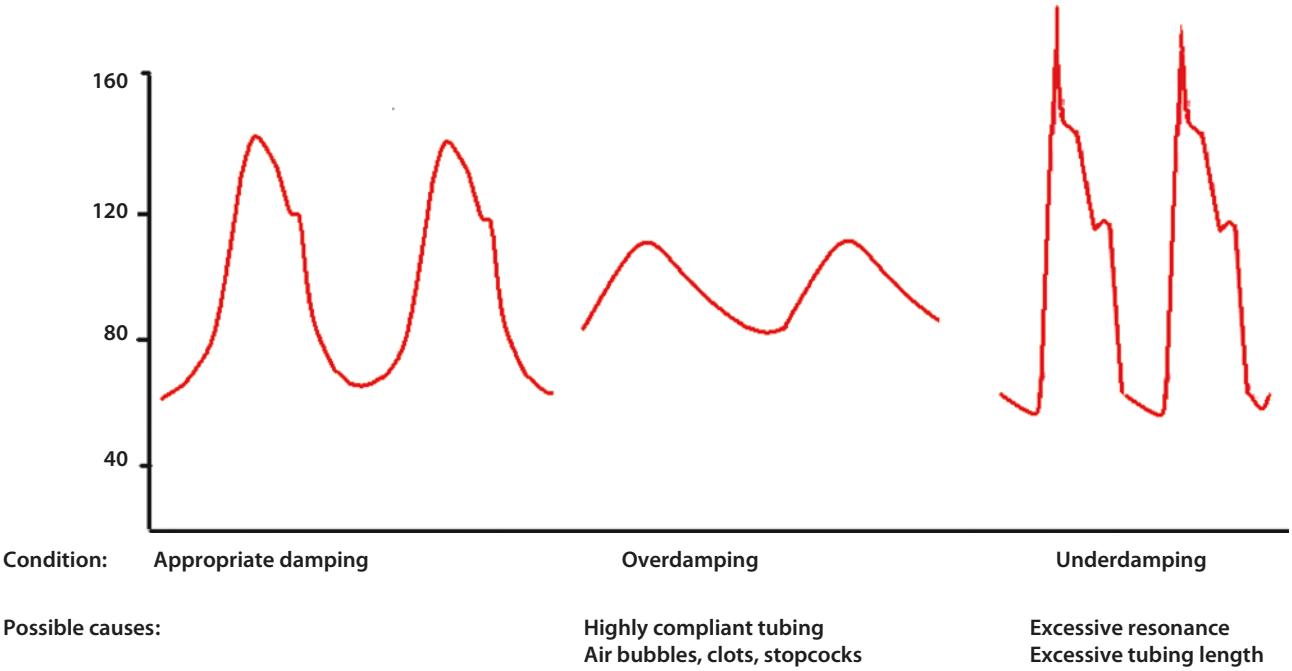


Fig. 16.6 Effect of damping on arterial waveform appearance

As a general rule, underdamped systems augment energy of the oscillating waves and artificially increase the system's output, whereas overdamped systems absorb energy and artificially decrease the system's output.

Fast Flush Test

The fast flush test allows for quantification of excessive resonance within the system.

Understanding that underdamped systems can lead to resonance, a simple bedside test can identify the presence of resonant waves. Delivering a small "fast flush" to the system allows quantification of excessive resonance within the system. The initial change on the arterial waveform monitor consists of a large square wave reflecting the abrupt and large pressure change the system has undergone due to the fast flush. The large square wave is followed by a series of resonant waves prior to returning to the arterial pressure wave. In an appropriately damped system, only one resonant wave is seen. In an underdamped system, multiple waves are seen prior to the return to the artificially elevated systolic pressure waveform (often due to excessive tubing length). In an overdamped system, no waves are seen (Fig. 16.7). There may be a rounded or scooped appearance on the tracing prior to returning to the artificially lowered systolic pressure waveform. This is often due to excessive tubing compliance, bubbles, or leaks.

Leveling and Zeroing

Arterial and central venous pressure monitoring devices must be leveled to the phlebostatic axis to have the contribution of hydrostatic pressure in the system negated. The phlebostatic axis is the external reference point of the atria and is found by locating the junction of the vertical line drawn down from the fourth anterior intercostal space (usually located near the nipple) and the horizontal midaxillary line (Fig. 16.8). Atmospheric pressure is discounted from the pressure measurement by opening the system to the atmosphere and calibrating the pressure reading to zero at the phlebostatic axis.

Failure to level the system results in an error due to the addition of hydrostatic pressure of the fluid in the column to the blood pressure transducer.

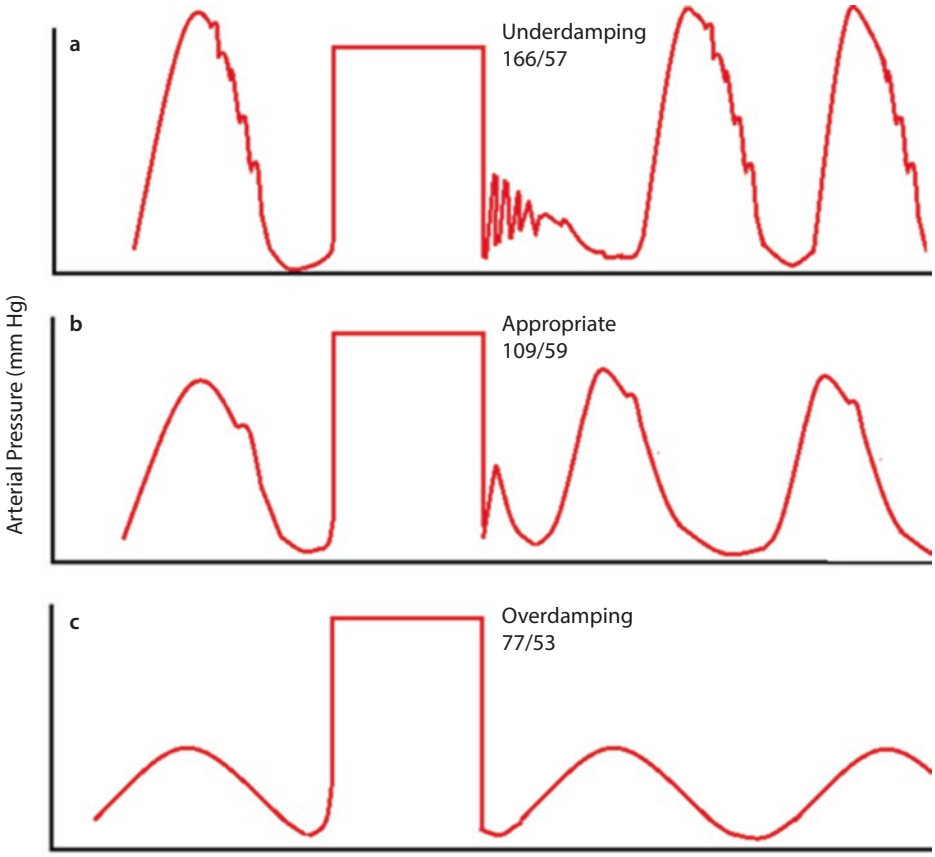


Fig. 16.7 Fast flush test to determine effect of damping. Panel **a** – Multiple resonant waves after fast flush indicative of underdamping, increased resonance, and artificial increase in systolic blood pressure and decreased diastolic blood pressure. Panel **b** – Appropriate degree of damping with one resonant wave evident after fast flush. Panel **c** – Absence of resonant waves and scoop after fast flush indicative of overdamping and artificial decrease in systolic blood pressure

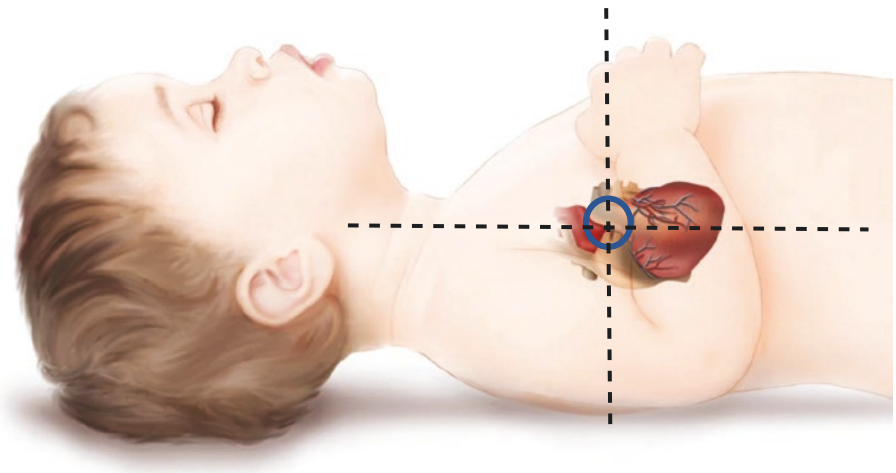


Fig. 16.8 Phlebostatic axis. Junction of vertical line down from the fourth intercostal space and the horizontal midaxillary line. Ana Truqui

Every 10 cm error in leveling can result in a 7.4 mm Hg error in the pressure measured. A transducer that is zeroed below the patient's heart produces falsely elevated pressures, whereas a transducer zeroed above the patient's heart produces falsely low pressures. Thus, when the patient's position is changed, the transducer position should be readjusted to the patient's phlebostatic axis.

16.2.1.2 Variations in Arterial Waveforms

Pulsus Paradoxus

Pulsus paradoxus is a true misnomer. It is not a paradoxical phenomenon but instead an exaggeration of a normal hemodynamic response to inspiration (Fig. 16.9). Pulsus paradoxus is defined as an exaggerated fall in systolic blood pressure, usually greater than 10 mm Hg (normal is about 5 mm Hg), occurring during a negative pressure inspiration. There are several mechanisms responsible for this fall in systolic pressure. It is important to appreciate these mechanisms in the healthy state to better understand how their effects are increased in pathological states such as hypovolemia, tamponade, and obstructive airway disease.

The normal fall in systolic pressure during inspiration is due to several hemodynamic events:

1. Inspiration causes pooling of pulmonary venous blood and therefore decreased left heart preload.
2. Inspiration causes increased venous return to the right heart. However, this is not immediately translated to increased LV preload. Instead, the increased right ventricular volume causes a further decrease in LV size and preload by the mechanism of *ventricular interdependence*. That is, the increased RV size causes septal shift to the left and hence transient decreased LV size.
3. Negative intrathoracic pressure relative to atmospheric pressure also causes an increase in ventricular transmural pressure leading to an increase in LV afterload.

Exaggerated falls in systolic pressure during inspiration occur in a variety of pathological states. In diseases that create lower airway obstruction (e.g., asthma), the greater negative intrathoracic pressure generated during inspiration accentuates the above effects. In addition, with air trapping and hyperinflated lungs, the diaphragm flattens, which tightens the pericardium around the

Pulsus paradoxus is not a paradoxical phenomenon but rather is an exaggeration of the normal fall in systolic pressure in response to the hemodynamic changes induced by negative pressure inspiration.

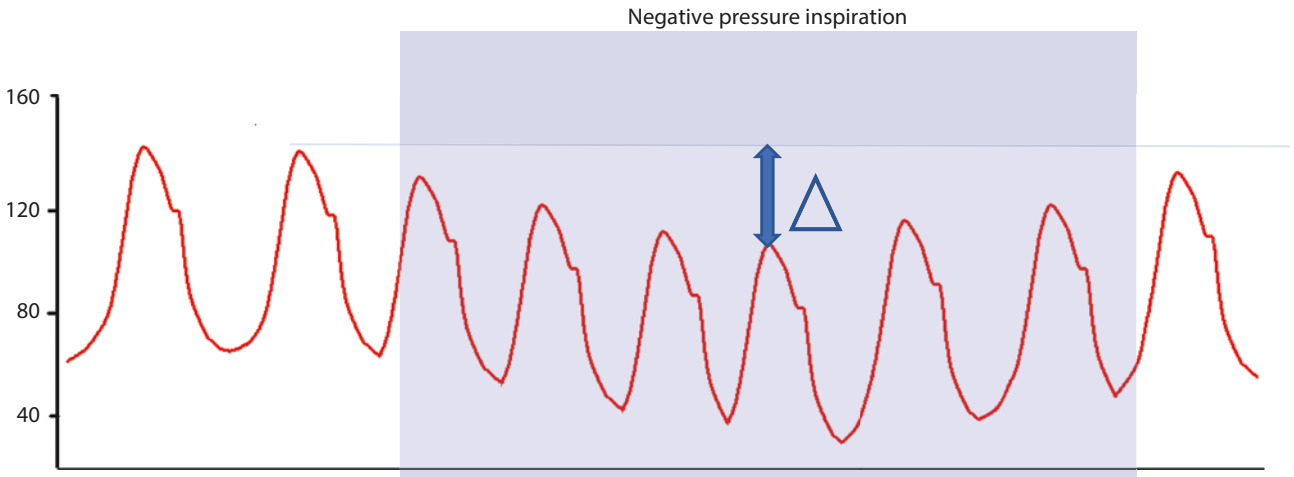


Fig. 16.9 Pulsus paradoxus occurs when the normal fall in systolic pressure due to inspiration (shaded area) is exaggerated to >10 mm Hg. Pulsus paradoxus is described during negative pressure breathing

heart limiting cardiac chamber size since the parietal pericardium attaches to the diaphragm. These changes lead to the characteristic narrow cardiac silhouette seen on chest x-ray. In tamponade states, compromised cardiac filling and the leftward septal bulging that occurs during inspiration further accentuate pulsus paradoxus. Any condition associated with hypovolemia and decreased circulating volume will also result in an exaggerated fall in systolic blood pressure during inspiration.

Systolic Pressure Variation

The hemodynamic principles that govern systolic pressure variation are similar to those in pulsus paradoxus. Instead of a fall in pressure during negative pressure breathing, there is an early rise in pressure during the inspiratory phase of positive pressure breathing.

Systolic pressure variation (SPV) refers to the arterial pressure waveform changes that occur during positive pressure mechanical ventilation. The hemodynamic principles are similar to those that create pulsus paradoxus, but instead of a fall in pressure during negative pressure breathing, there is a rise in pressure during the inspiratory phase of positive pressure breathing. At times, this phenomenon is referred to as *reverse pulsus paradoxus*; however, *systolic pressure variation* is the preferred term.

A single positive pressure breath normally affects the arterial pressure in a biphasic manner (Fig. 16.10). The initial hemodynamic effect of a positive pressure breath is to "squeeze" pulmonary vascular blood into the LA leading to an increase in LV preload and systolic pressure. In addition, positive intrathoracic pressure reduces the afterload on the LV further augmenting this early rise in arterial pressure. This is referred to as the Δ up component of *SPV*. Note that while LA preload is augmented early in the positive pressure breath, the RA preload is decreased as the positive intrathoracic pressure decreases venous return. Following the Δ up, a fall in systolic pressure follows due to the initial decreased venous return to the right heart "catching up," and ultimately, result-

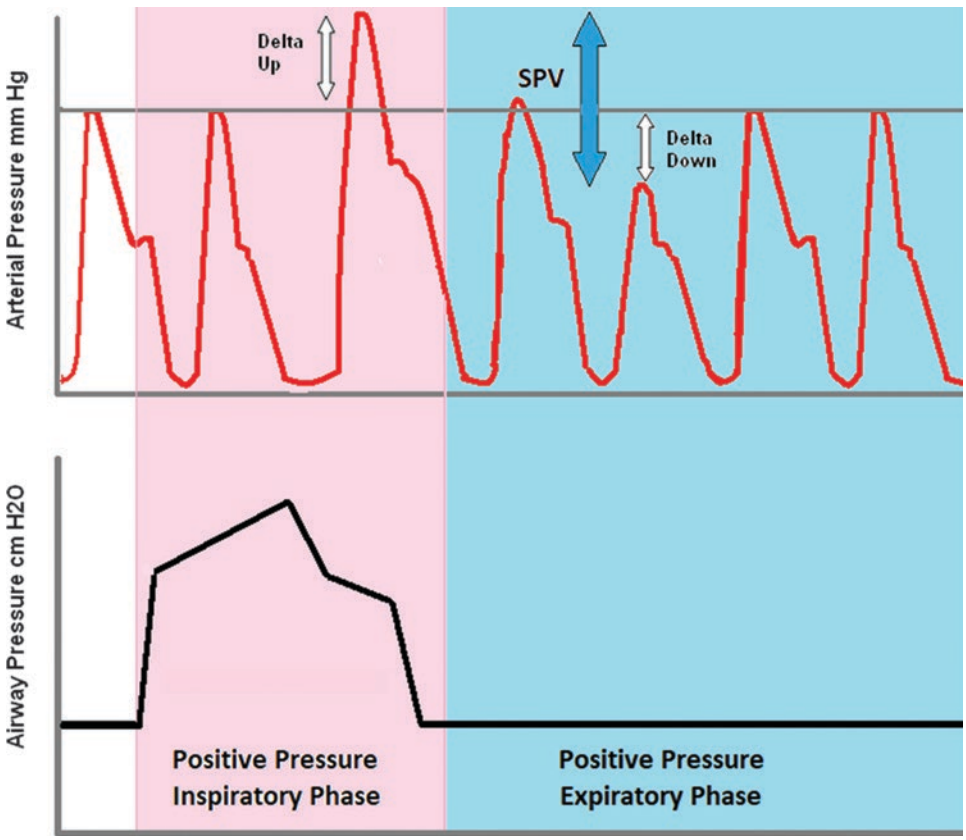


Fig. 16.10 Systolic pressure variation (SPV) during single positive pressure breath. *Delta up* – Increase in systolic pressure at the initiation of positive pressure breath. *Delta down* – Decrease in systolic pressure occurring during expiratory phase of a positive pressure breath. SPV = sum of delta up and down

ing in decreased left-sided preload. The reduction in LV preload and output leads to a smaller LV stroke volume and a brief reduction in arterial pressure that occurs during the expiratory phase of a positive pressure breath (Δ down).

An increased SPV (>10 mm Hg) can occur if the Δ down component is lowered or if the Δ up component is elevated. Hypovolemia has been found to cause an increased SPV (>10 mm Hg). Positive pressure amplifies the effects of decreased effective circulating volume and causes a greater fall in the Δ down component of SPV secondary to a substantial decline in venous return. Several adult studies demonstrated that an increase in the SPV occurs prior to a fall in arterial pressure and may be predictive of clinically significant hypovolemia. Excessive positive pressure during mechanical ventilation can also increase the magnitude of the Δ down component by compromising venous return in patients without hypovolemia.

The Δ up component of SPV reflects augmentation of systolic blood pressure early in the positive pressure breath due to an initial increase in LV preload and decrease in LV afterload. The Δ down reflects a fall in systolic pressure during the expiratory phase of the positive pressure breath as decreased venous return to the RV results in a subsequent decrease in LV preload.

During a positive pressure breath, an increased SPV due to an increased initial Δ up component may be observed in the setting of myocardial dysfunction. This increased SPV is not due to hypovolemia; rather, it reflects improved left ventricular ejection secondary to reducing left ventricular afterload with each positive pressure breath.

During mechanical ventilation, an increased delta down component of the systolic pressure variation can be associated with decreased preload due to hypovolemia and/or excessive positive pressure.

The measurement of SPV in mechanically ventilated children is an excellent example of *functional hemodynamic assessment*. Traditionally, many hemodynamic measurements, such as central venous pressure and pulmonary capillary wedge pressure, have been static values obtained by bedside measurement of invasive pressures. When hemodynamic measurements are taken in the context of a physical maneuver (e.g., application of a positive pressure breath, straight leg raise) or a therapeutic challenge (e.g., volume infusion), the hemodynamic data are dynamic and may provide far more useful information than static measurements alone.

Commonly used dynamic measurements are based on beat-to-beat changes in LV output during positive pressure ventilation. Measures such as stroke volume variation, pulse pressure variation, and systolic pressure variation have been found to be clinically reliable variables for predicting fluid responsiveness in adults. These measurements have not been extensively studied in children; however, a recent meta-analysis suggests that stroke volume variation was of diagnostic value in predicting fluid responsiveness in children undergoing positive pressure ventilation.

Functional hemodynamics such as systolic pressure variation are measurements taken in the context of a physical maneuver (e.g., application of a positive pressure breath, straight leg raise) or therapeutic challenge (e.g., volume infusion).

16.2.1.3 Complications of Invasive Arterial Pressure Monitoring

There are multiple complications that may occur during placement and maintenance of an arterial line (◘ Box 16.1). A large retrospective pediatric cohort study demonstrated that up to 10% of indwelling arterial lines resulted in complications. The number of complications is significantly greater if arterial line malfunction is also considered. Two complications that deserve special consideration are ischemia and infection.

Box 16.1 Complications of Arterial Cannulation

Arterial line complications

- Vasospasm
- Distal ischemia
- Arterial thrombosis
- Embolism (air, clot, or other material)
- Infection
- Hematoma
- Hemorrhage from inadvertent disconnection
- Nerve injury
- Aneurysm formation

Ischemic Injury

Indwelling peripheral artery catheters allow continuous recording of blood pressure and access to arterial sampling. Maintaining an indwelling catheter is relatively safe with a very low incidence of permanent distal ischemic injury. Several interventions that attempt to mitigate the risk of ischemia include Allen testing for collateral flow when placing a radial line, continuous infusion of low-dose heparin, in-line air filter, and utilizing papaverine as an antispasmodic.

Although vascular supply to the hand varies greatly, adequate collateral flow is present in most children. Procedures that use the radial artery as an entry site for cardiac catheterization have provided new insight into the assessment of ulnar collateral blood flow to the hand – specifically the utility of the Allen test. The modified Allen test has been the most frequently used method to clinically assess adequacy of ulnar artery collateral flow. It is performed by instructing the patient to clench his/her fist, or if the patient is unable, the hand is closed tightly. Direct occlusive pressure is applied to both the ulnar and radial arteries, thereby temporarily obstructing blood flow to the hand. Blanching of the palm and fingers should occur. The occlusive pressure on the ulnar artery is released, and the hand should reperfuse and flush within 5–10 s. Flushing denotes that the ulnar artery is patent and provides adequate collateral blood flow. If the hand does not flush, the ulnar circulation is inadequate, and the radial artery should not be instrumented. However, the utility of the modified Allen test has been questioned, and it may have no direct correlation with ischemic complications of radial artery catheterization. It is a subjective clinical test that lacks interobserver reliability. Multiple reports documented adequate collateral flow via Doppler or angiography when the modified Allen test suggested a lack of ulnar collateral flow. Its use may be limited as a bedside screening test. An Allen test that demonstrates no collateral flow from the ulnar artery may not preclude the use of a radial arterial line. A Doppler or angiographic study should be obtained to verify an Allen test that suggests no collateral flow.

The use of a continuous saline infusion with a low-dose heparin (e.g., 1–2 units heparin/mL at 3 mL of flush solution per hour) has been utilized in children with indwelling arterial catheters. The practice is commonly used in adults; however, a 2014 meta-analysis revealed the cumulative adult evidence is of poor quality and does not provide sufficient evidence to support the practice. Pediatric evidence suggests there is a benefit of continuous infusion of saline over intermittent manual flushing of arterial catheters; however, data regarding the addition of low-dose heparin is not conclusive.

The radial, femoral, axillary, dorsalis pedis, and posterior tibial arteries are commonly used sites for arterial line placement. The placement of an arterial catheter in the brachial artery traditionally has been avoided due to lack of sufficient collateral flow. However, adult and pediatric studies reported that brachial artery catheterization may not carry an increased risk of ischemic complications as previously believed. Nonetheless, until larger studies are conducted regarding the safety of brachial artery catheterization, it should not be used as a primary site for intra-arterial pressure monitoring.

Infection

Arterial catheters traditionally were thought to have a lower infection rate compared to venous catheters due to the high flow and oxygen tension present in arteries. However, the incidence of arterial-related catheter infection is similar to rates observed in central venous catheters; infection rates of 1–7% have been reported. Young age and the femoral site appear to increase the risk of infection. As with central venous catheters, the risk increases incrementally with the duration of catheter use. Understanding the impact that bloodstream infections have on intensive care morbidity and mortality, arterial catheters should be treated with the same vigilance as central venous catheters. Methods

to decrease infections from arterial catheters should include selective use, early removal, and adherence to proven protocols to assure appropriate insertion and maintenance techniques.

Vasospasm and Catheter Malfunction

Maintaining indwelling catheter patency and function can be challenging, especially in infants.

Providing continuous fluid flowing through the catheter and careful serial assessments are accepted practices. Papaverine is a direct arterial vasodilator that has been used extensively in the neonatal population to decrease vasospasm induced by peripheral arterial catheters. Limited data suggests papaverine (30 mg/250 mL) added to the continuous saline infusion may prolong the patency of peripheral arterial catheters in children and neonates.

16.2.2 Central Venous Pressure Monitoring

The central venous pressure (CVP) may provide important hemodynamic data in a variety of disease states encountered in the PICU. In addition, it provides a route for monitoring central venous oxygen saturation, which helps assess perfusion as discussed later in this chapter. The optimal site for monitoring CVP is at the junction of the superior vena cava and the upper portion of the right atrium (RA). CVP varies with changes in intrapleural pressures. The measured CVP most closely approximates transmural filling pressures at end-expiration when the intrapleural pressure approaches atmospheric pressure.

A CVP can reflect right ventricular end-diastolic pressure (RVEDP), which has been used to estimate right ventricular end-diastolic volume (RVEDV). The RVEDP is dependent on the underlying status of the RV; hence:

$$\text{RVEDP} = \text{RVEDV} \times \text{RV compliance}$$

CVP provides information regarding RVEDP but may not accurately predict the RVEDV or how the ventricle will respond to volume administration.

It is critical to appreciate that CVP provides information regarding RVEDP; however, it may *not* accurately predict the RVEDV or how the ventricle will respond to volume administration. Right ventricular end-diastolic volume is affected by tricuspid regurgitation and poor ventricular compliance, both of which may be present in hemodynamically unstable children. Although CVP is clinically used to assess cardiac preload, multiple adult studies have proven that CVP does not correlate well with RVEDV. Changes in right ventricular compliance may affect right atrial pressure and volume in a manner that is difficult to predict. Although very high or very low values for the CVP may provide important data regarding the volume status of the RV, most intermediate CVP readings provide little clinically useful information.

In addition to its numerical value, the CVP waveform can provide clues to clinical conditions including arrhythmias, atrioventricular (AV) valve dysfunction, and tamponade states. The normal CVP waveform reflects the right heart events that occur during the cardiac cycle (Fig. 16.11). The first and most prominent positive deflection is the ***a wave***, which represents the increase in intra-atrial pressure observed during atrial contraction. Atrial contraction occurs at the end of ventricular diastole and marks the start of ventricular systole. The atrial contraction serves to "top off" ventricular filling and can contribute significantly to cardiac output, especially when ventricular function is reduced. The decline in atrial pressure after atrial contraction is interrupted by the next positive deflection termed the *c wave*. This bump in pressure reflects the displacement of the tricuspid valve up toward the atrium during isovolumic ventricular contraction. The pressure in the atrium then declines during atrial relaxation. The downward displacement of the tricuspid valve that occurs during ventricular contraction further reduces atrial pressure and is *reflected in the x descent* of the CVP waveform.

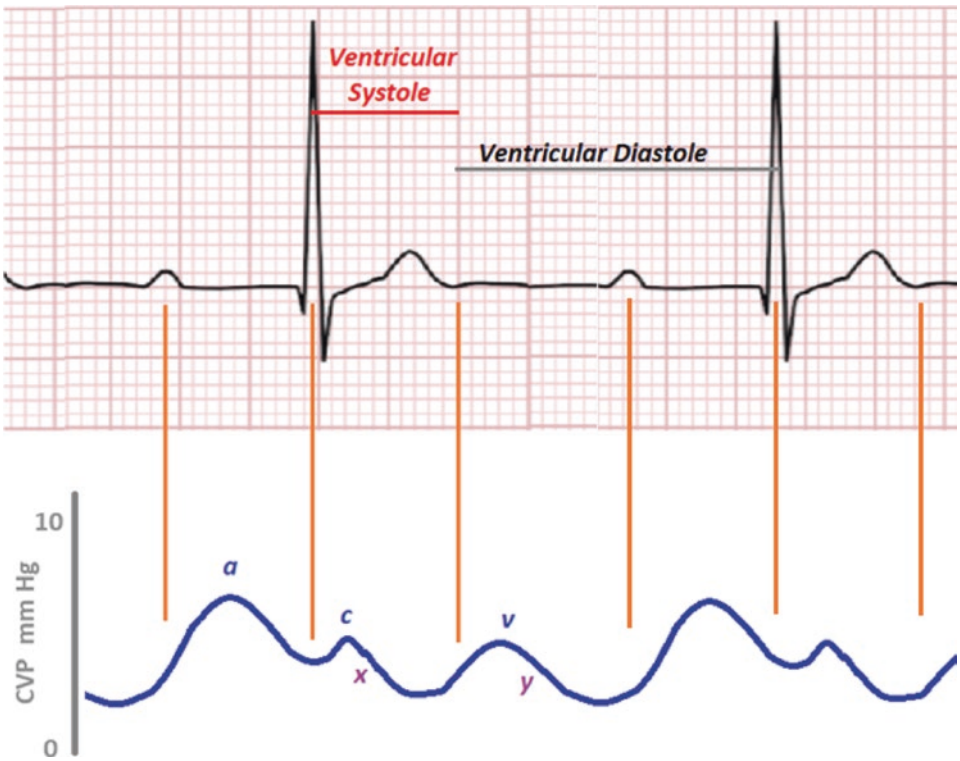


Fig. 16.11 Components of central venous pressure waveform with corresponding electrocardiogram

Following the *x descent*, atrial pressure rises slowly during the end of ventricular systole as the atrium fills with venous blood from the inferior and superior vena cava and is reflected in the *v wave*. After atrial filling, the tricuspid valve opens and a fall in atrial pressure occurs as the atrium is drained (*y descent*). The *a wave* follows again as the atrium contracts to "top off" the ventricle. The *a wave* occurs after the P wave of the ECG. The c wave, if present, occurs at the end of the QRS complex and the v wave occurs after the T wave of the ECG. To obtain a numerical value of the CVP, it is best to measure the mean pressure of the *a wave*.

16.2.2.1 Variations in CVP Waveform

Various conditions can be diagnosed or confirmed by careful examination of the CVP waveform. Arrhythmias can produce characteristic changes in the waveform. AV dissociation will cause significant elevations in atrial pressure as asynchronous atrial contraction occurs against a closed tricuspid valve. These elevations are referred to as *cannon a waves* on the CVP tracing (Fig. 16.12). They can also be seen during ventricular pacing where normal atrioventricular synchrony is lost. Large *a waves* may be also seen with a poorly compliant RV or in the setting of tricuspid stenosis.

Atrial fibrillation causes the a wave to be lost and the c wave to become more prominent. This is due to a greater atrial volume present at the onset of ventricular systole because of the absence of effective atrial contraction and emptying.

Multiple causes of large a waves on a CVP tracing include AV dissociation, RV noncompliance, asynchronous pacing, and tricuspid stenosis.

Tricuspid regurgitation causes additional filling of the atrium through the incompetent valve during ventricular isovolumic contraction and ejection. The CVP waveform will display an exaggerated c and v wave with an attenuated x descent, sometimes referred to as a cv wave. The entire waveform becomes "ventricularized" during severe tricuspid regurgitation and resembles the right ventricular pressure tracing (Fig. 16.13).

Tamponade physiology causes elevation of the CVP and equalization of diastolic filling pressures (CVP = RVEDP = PADP = PAWP). The *y descent* may be lost or blunted, owing to restricted ventricular filling due to a reduced chamber size and high diastolic pressures.

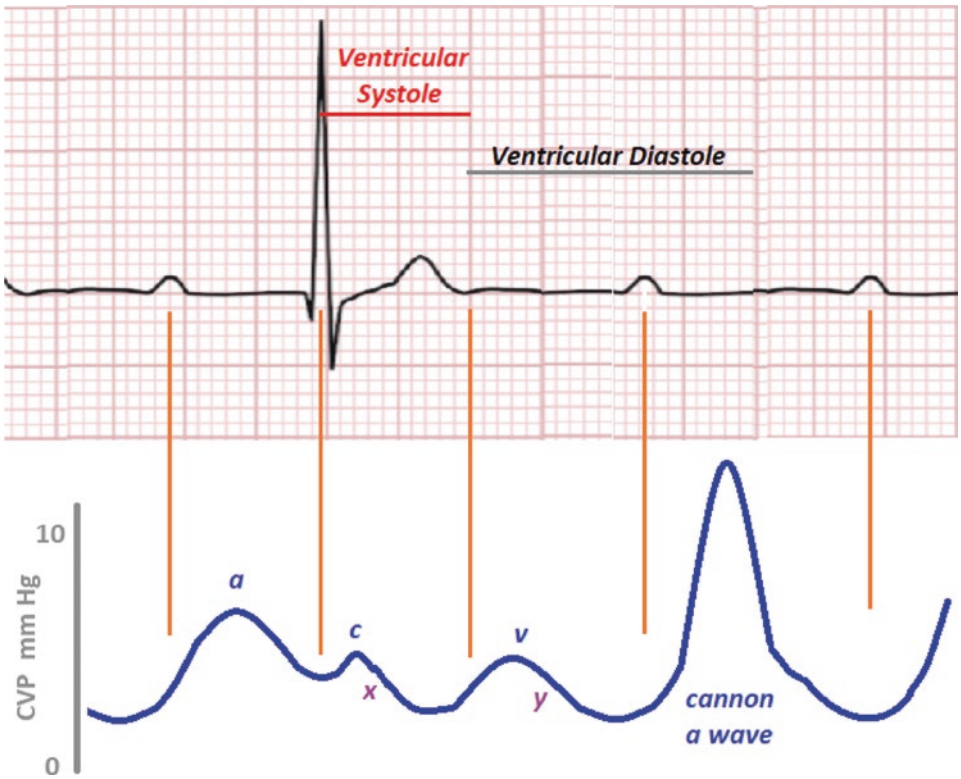


Fig. 16.12 Enlarged a waves, often referred to as cannon a waves, can be seen in arrythmias that produce atrioventricular dissociation. Examples include junctional rhythm, asynchronous cardiac pacing and complete AV block as seen in figure

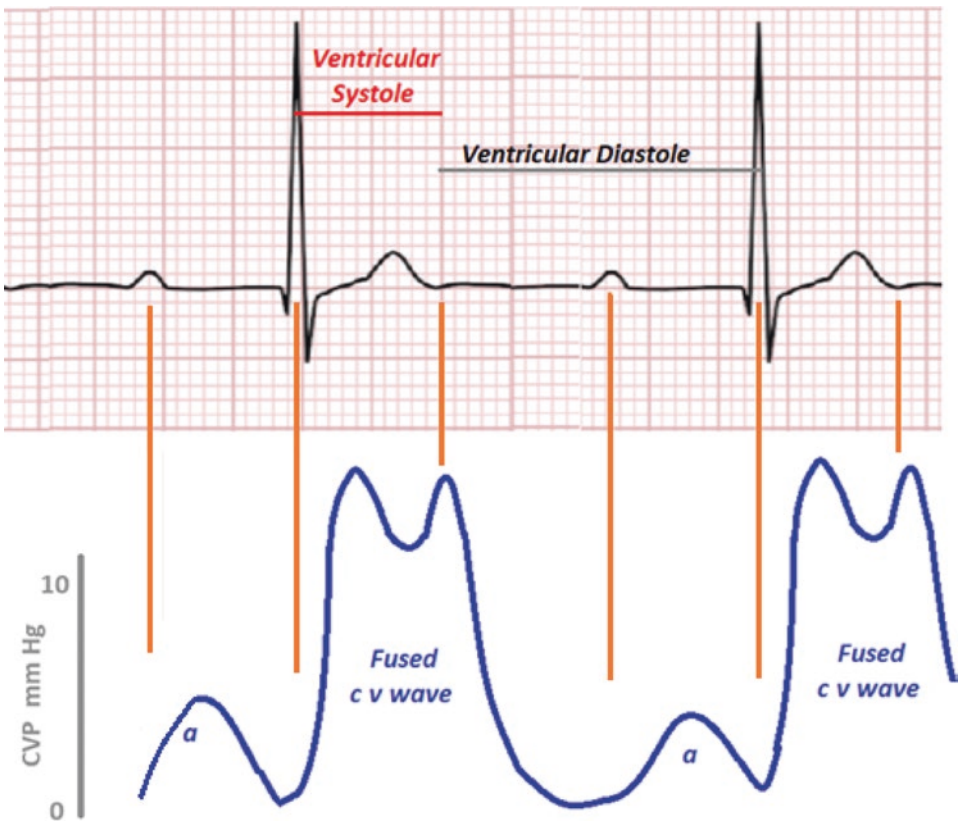


Fig. 16.13 Central venous pressure waveform demonstrating severe tricuspid regurgitation. Regurgitant blood entering the atrium during RV contraction results in an increased c and v waves (also referred to as the cv wave)

16.2.2.2 Complications of Central Venous Catheters

The placement of a central venous catheter (CVC) can be associated with significant morbidity. The placement should only occur after careful evaluation of CVC necessity and should never be deemed routine. Up to 15% of patients with central venous catheters experience complications. These complications can be categorized as mechanical, infectious, or thrombotic (Box 16.2).

Mechanical complications are more common when using the subclavian and internal jugular approach. Pneumothorax is of particular concern during subclavian cannulation. Cannulation of the right subclavian vein may offer some theoretical advantage as the lung apex is lower on the right and injury to the left-sided thoracic duct is avoided.

Although any CVC site is associated with a risk of both local infection and central line-associated bloodstream infection (CLABSI), the femoral site in postpubescent children is associated with an increased risk. CVC infections are more likely to occur during the maintenance of the catheter rather than during insertion of the catheter. Immunocompromise states and prolonged duration of catheter use substantially increase the CLABSI risk. Detailed review of CLABSI definitions, risks, prevention, and treatment is covered in ▶ Chap. 37, "Nosocomial Infections."

Box 16.2 Complications of Central Venous Catheters

Mechanical

- Arterial puncture
- Catheter occlusion due to precipitants
- Hematoma
- Hemorrhage (increased risk with coagulopathy)
- Pneumothorax/hemothorax (subclavian, internal jugular approach)
- Retention of foreign body (guidewire, catheter fragment)
- Arrhythmia
- Cardiac puncture/tamponade
- Non-thrombotic occlusion (kink)

Infectious

- Local site infection (cellulitis, thrombophlebitis)
- Central line-associated bloodstream infection (CLABSI) (bacteremia, sepsis)

Thrombotic

- Catheter occlusion due to thrombosis
- Venous thrombosis
- Embolization of thrombi

Occlusion by a thrombus within the catheter lumen is common, occurring in up to one-third of children with CVCs. The fibrinolytic tissue plasminogen activator (t-PA) has high efficacy and low risk in treating CVC occlusions in children. Several pediatric trials have found that t-PA, also known as alteplase, administered and allowed to dwell produced catheter clearance rates of over 80%. Typical pediatric alteplase doses range from 0.5 to 2 mg instilled into the lumen with dwell times ranging from 1 to 4 h followed by aspiration.

Owing to an increased use of CVCs, the rate of catheter-related venous thrombosis (CRVT) has increased dramatically over the last 20 years. CRVT is the most frequent cause of pediatric deep vein thrombosis. There are multiple factors that place the critically ill child at risk for CRVT (Box 16.3). The incidence of CRVT is increased in children who are prothrombotic (e.g., malignan-

cies) and those at risk for hyperviscosity (e.g., severe dehydration secondary to diabetic ketoacidosis). Small vessel size in relation to catheter size and venous stasis also have been implicated as conditions increasing CRVT risk in children. Technical issues during insertion play a significant role in thrombus initiation. Multiple failed attempts cause endothelial injury and tissue factor release from damaged endothelium. Tissue factor (thromboplastin) forms a complex with factor VIIa and activates factor IX and X, thereby initiating a procoagulant cascade that generates thrombin. Thrombin is a potent platelet activator. Activated platelets arrive at the area of endothelial injury and act to propagate the thrombus.

All mechanical, infectious, and thrombotic complications of CVCs can be dramatically reduced by a methodical approach to their insertion and maintenance. Evidence-based bundles that guide selection of sites, utilize ultrasound guidance during insertion, maximize adherence to aseptic techniques during maintenance, and promote daily review of line necessity will have the greatest impact in reducing institutional CLABSI rates.

CVC necessity should be reviewed daily. The risk of CLABSIs increases with the duration of time the catheter is left in place.

Box 16.3 Factors Increasing Risk of Catheter-Related Thrombosis

Underlying disease
- Malignancy
- Sepsis
- Hypercoagulable states (e.g., malignancy, nephrotic syndrome, cyanotic congenital heart disease, sepsis, endogenous anticoagulant deficiency)
- Dehydration (e.g., diabetic ketoacidosis)

Multiple initial attempts
Prolonged duration of use
Use of hyperosmolar solutions
Immobility
Procoagulant medications (e.g., oral contraceptives)

16.2.3 Invasive Measurement of Cardiac Output

Physical examination, waveform analysis, biochemical markers, and imaging provide indirect assessments of cardiac output (CO). At times, direct measurement of CO and specific intracardiac hemodynamic data is required. A review of the principles behind CO determination is important in understanding the utility and limitations of directly measuring CO. The following principles will be discussed:
- Conservation of mass
- Dye dilution method of determining cardiac output
- Thermodilution method of determining cardiac output
- Fick method of determining cardiac output

16.2.3.1 Conservation of Mass

The law of conservation of mass states that mass can neither be created nor destroyed but that it can be changed. The conservation of mass states that what comes out of a system must equal what went into the system plus or minus any change that occurred in between. Using this principle, the measurement of an unknown volume in a static system, such as a glass beaker, can be determined. If a substance is added to a solution, and the initial and final concentrations of the substance in the solution are known, then the volume of the beaker can be solved mathematically by:

$$\text{Volume}\ (\text{L}) = \frac{\text{Amount of substance added}\,(\text{gms})}{[\text{Final concentration}\,(\text{gms/L}) - \text{Initial concentration}\,(\text{gms/L})]}$$

Using the law of conservation of mass as a foundation, cardiac output can be determined by the dye dilution, thermodilution, or the Fick method.

16.2.3.2 Dye Dilution

In a non-static system, flow (Q) can be determined using the same conservation of mass principle. Instead of determining the static volume, the dynamic variable of flow can be determined in the following manner: A known amount of a substance is added to a flowing solution upstream and the change in concentration of the solution is determined by continuously plotting the concentrations from its first appearance (t_1) to its downstream disappearance (t_2) and then calculating the area under the curve (Fig. 16.14). The flow of a system can be solved mathematically by:

$$Q(\text{L/min}) = \frac{\text{Amount of substance}\,(\text{mg})}{\text{Average Concentration}\,(\text{mg/L})(t_2\ \text{min} - t_1\ \text{min})}$$

The equation to determine flow in a dynamic system essentially describes the dye dilution method for determining cardiac output. Substance I is the indicator dye that is injected into the venous side of the circulation ("upstream"). The heart serves as a mixer of the dye and sampling of the dye occurs at a distal artery ("downstream," which can be the pulmonary or systemic artery) where t(s) is the time in seconds between the initial and final sampling of the indicator dye concentration:

$$\text{CO}(\text{L/min}) = \frac{I\ \text{amount}\,(\text{g}) \times 60\,\text{s/min}}{\text{Concentration}\,(\text{g/L}) \times t\,(\text{s})}$$

Measurement of the dye in the distal artery is complicated by the recirculation phenomenon. Concentration of the dye will peak early on and subsequently drop off as the slower particles arrive. However, before all the slower ones

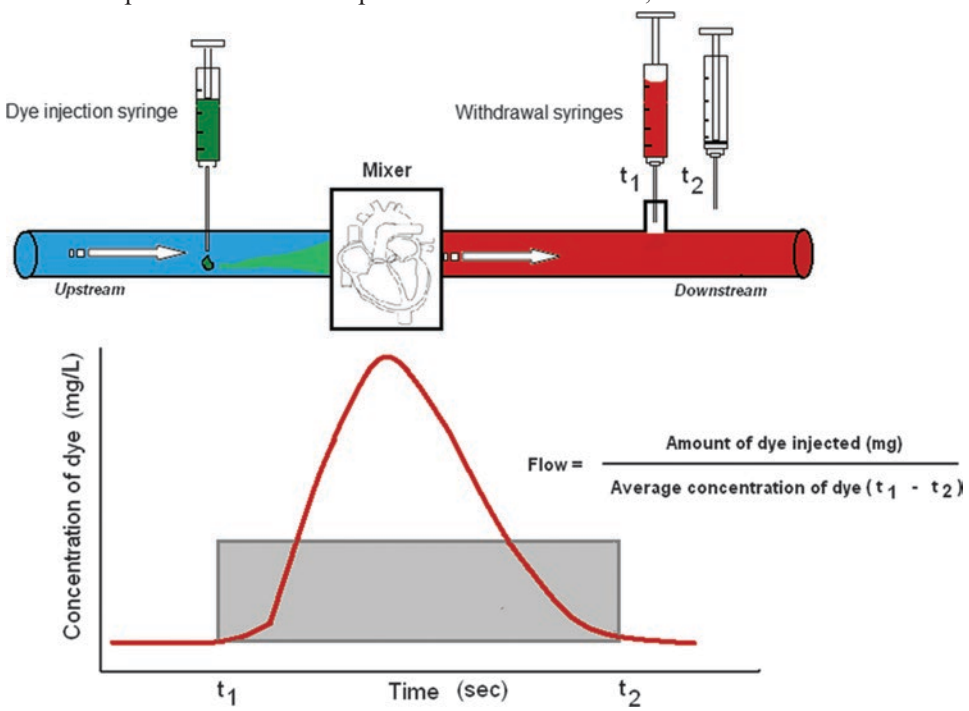


Fig. 16.14 Determination of flow using conservation of mass law. The flow of a system is determined by plotting changes in concentration of an added substance (dye) over time. Dye is added upstream to flowing venous blood. The dye is uniformly mixed by the heart. The concentration of the dye is measured serially downstream from the arterial port. Time one (t_1) is the time the dye is first detected and time 2 (t_2) is the time when it disappears. The average concentration of the dye over time is depicted in the gray box. Flow is determined using the modified conservation of mass equation

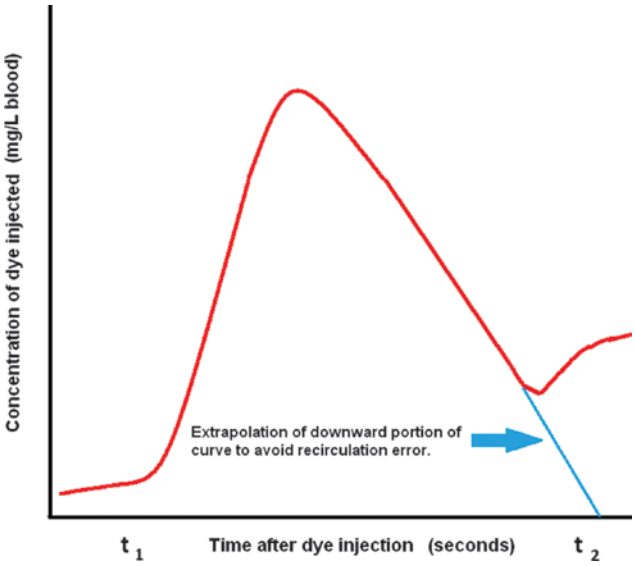


Fig. 16.15 To avoid error due to recirculation of dye, the downslope of the area under the curve is mathematically extrapolated to determine t_2

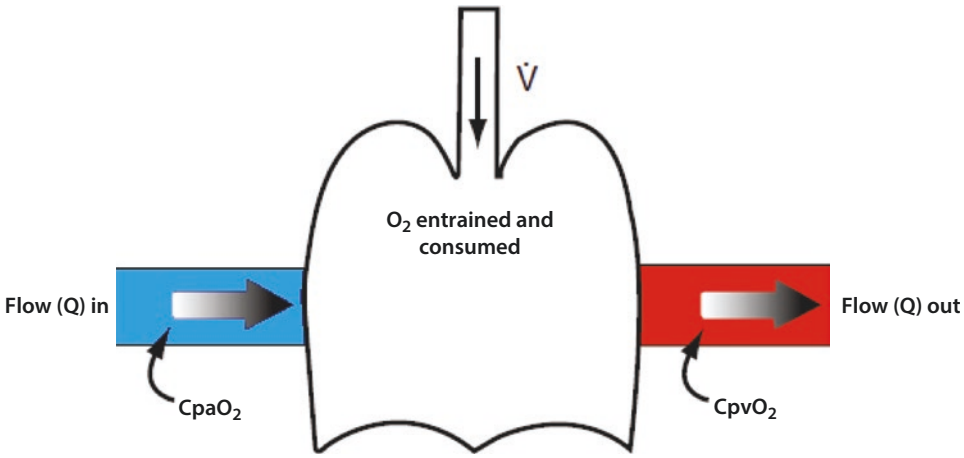


Fig. 16.16 Fick method for determination of cardiac output by using oxygen as the physiologic indicator. $C_{pa}O_2$ and $C_{pv}O_2$ are the oxygen content of pulmonary artery and pulmonary venous blood, respectively

arrive, the faster particles recirculate causing a falsely elevated value for the arterial concentration. To correct for this recirculation phenomenon, the downslope of the curve is extrapolated (Fig. 16.15).

16.2.3.3 Fick Method

In 1870, Adolph Fick, using the conservation of mass principle, described a physiological method of determining CO. Instead of using a dye as the "indicator," oxygen is used. He postulated, in a steady state, the quantity of oxygen in the pulmonary veins should equal the amount entering the lung via the pulmonary artery plus the amount of oxygen entrained during breathing (Fig. 16.16).

Cardiac output is calculated using the Fick method by accounting for flow (Q) and oxygen content (C_xO_2) on both ends of the circuit. For the pulmonary circuit, the "in" is equal to the pulmonary blood flow (Q_{pul}) multiplied by the pulmonary artery content of oxygen ($C_{pa}O_2$) plus the entrained oxygen from the lungs, which at steady state equals the oxygen consumed by the body's metabolism (VO_2). The VO_2 is the difference between the oxygen delivered to the tissue (arterial side) and the oxygen returned by the tissue (venous side). Since oxygen is added to blood across the pulmonary circuit, the entrained oxygen is added to the input.

The "out" is equal to the pulmonary blood flow (Q_{pul}) multiplied by the pulmonary vein content of oxygen ($C_{pv}O_2$). Since the output must equal the input plus or minus any change that occurred within the system, the equation can be described mathematically as:

$$\left[Q_{pul}\left(C_{pa}O_2\right)\right] + VO_2 = Q_{pul}\left(C_{pv}O_2\right)$$

$$\text{Solving for } Q_{pul}: \quad Q_{pul} = \frac{VO_2}{C_{pv}O_2 - C_{pa}O_2}$$

Systemic blood flow (Q_{syst}) can be similarly calculated. Assuming right heart output equals left heart output and the change in oxygen content across the systemic circulation equals ($C_{Ao}O_2 - C_{pa}O_2$), then Qsyst can be described mathematically as:

$$\text{Solving for } Q_{syst}: \quad Q_{syst} = \frac{VO_2}{C_{Ao}O_2 - C_{pa}O_2}$$

- $C_{Ao}O_2$ = aortic O_2 content (may also use distal arterial sample)
- $C_{pa}O_2$ = pulmonary artery O_2 content (may also use right atrial-superior cava junction sample)

If the PA is unable to be sampled, blood from the superior portion of the RA can be used. Sampling from the inferior RA should be avoided as it may result in a lower calculated oxygen content due to the entrainment of poorly saturated coronary venous blood in the sample. Furthermore, during shock states, sampling in the low portion of the RA may result in lower oxygen saturations than a true mixed venous saturation due to the inflow of poorly saturated IVC blood (see below discussion on mixed venous and central venous oxygen saturations).

Assuming no intracardiac shunt and ignoring the relatively low coronary artery blood flow returning to the right atrium via the coronary sinus, blood flow through the lungs is virtually equal to that through the body, that is, $Q_{pul} = Q_{syst}$ = cardiac output:

$$CO = \frac{VO_2}{C_{Ao}O_2 - C_{ra}O_2}$$

Measurement of cardiac output by the Fick method requires independent measurement of oxygen consumption (e.g., indirect calorimetry) or an assumption of normal oxygen consumption. The former is cumbersome, and the latter is not accurate since oxygen consumption varies greatly with critical illness. Due to these limitations, the Fick method is not routinely used as a bedside tool to calculate CO.

If an intracardiac shunt is present, the magnitude of the shunt can be calculated as Q_{pul}/Q_{syst}:

$$\frac{Q_{pul} = \dfrac{VO_2}{C_{pv}O_2 - C_{pa}O_2}}{Q_{syst} = \dfrac{VO_2}{C_{Ao}O_2 - C_{pa}O_2}}$$

Note that the estimation of the intracardiac shunt fraction does not require measurement of VO_2; it is expressed as follows after canceling VO_2, cross multiplying, and substituting oxygen saturation for oxygen content:

$$Q_{pul} / Q_{syst} = \frac{Sat_{Ao} - Sat_{ra}}{Sat_{pv\,or\,la} - Sat_{pa}}$$

The identification and quantification of a left to right (L to R) shunt can be of critical importance in understanding a child's underlying hemodynamic status. In the absence of lung disease, $Sat_{pv\ or\ la}$ is assumed to be 100%. Calculation of Q_{pul}/Q_{syst} may identify an otherwise unappreciated L to R lesion (e.g., PDA or major aortopulmonary collateral arteries). Postoperatively, the presence of an unexpected shunt following congenital heart disease surgery may reflect a residual lesion that requires repair (e.g., patch leak across a repaired VSD). The degree of a surgically created left to right shunt (e.g., modified Blalock-Taussig shunt) can also be quantified. $Q_{pul}/Q_{syst} > 1$ is indicative of some degree of L to R shunting. Generally, a Q_{pul}/Q_{syst} of > 2/1 is considered clinically significant.

16.2.3.4 Thermodilution

The thermodilution method to calculate CO utilizes the same fundamental principles employed in the derivation of the Fick equation. Rather than a change in dye concentration or oxygen content over time, thermodilution uses a change in blood temperature over time. Cardiac output can be determined using this method during right heart catheterization. In the absence of intracardiac shunting, right heart CO should equal left heart output. To perform thermodilution CO measurement, a fixed volume of fluid with a known temperature is injected into the right atrium. The downstream change in temperature is measured in the distal pulmonary artery. The change in temperature is plotted against time to generate a thermodilution curve (Fig. 16.17).

Using the data derived from the thermodilution curve, the CO can be calculated using the Stewart-Hamilton formula:

$$CO = \frac{V_1 (T_B - T_I) K_1 K_2}{\int (\Delta T_B dt)}$$

- V_1 = injectate volume
- T_B = blood temperature
- T_I = injectate temperature
- K_1 = empiric factor used to correct for warming of injectate through catheter
- K_2 = computation constants for the specific gravity and specific heat of blood and the injectate
- $\int \Delta T_B dt$ = change in blood temperature over time (AUC)

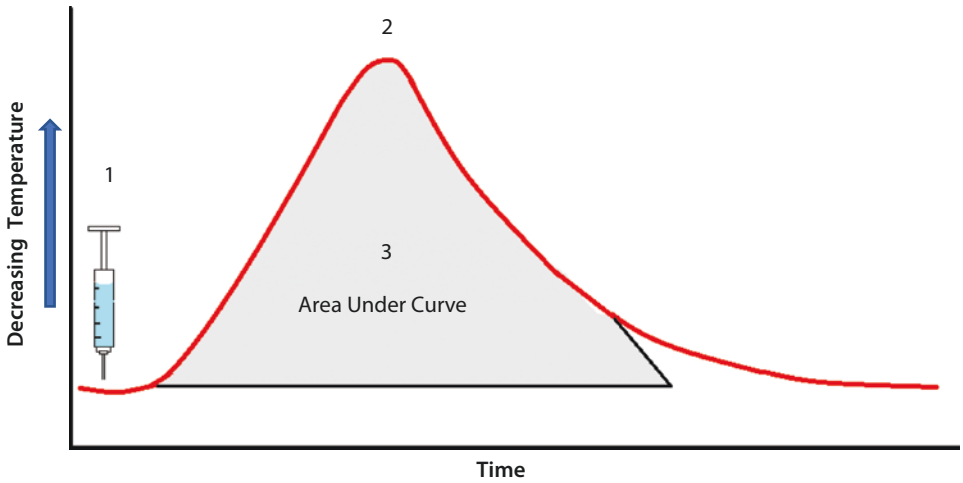


Fig. 16.17 Thermodilution curve. The curve represents a change from warmer blood temperature to cooler (due to the cold injectate) and then back to warmer temperature. 1. Bolus cold saline injected. 2. Peak temperature change which corresponds to the maximal amount of cooling ("thermodiluting") of the blood. 3. Calculated area under the curve. A normal curve characteristically shows a sharp upstroke from rapid injection of the injectate

16.2.3.5 Pulmonary Artery Catheterization

In 1970, Swan, Ganz, and colleagues introduced the use of bedside right heart catheterization for hemodynamic monitoring. Placement of a pulmonary artery catheter (PAC) allows for serial measurement of important cardiovascular parameters including cardiac output and intracardiac pressures. The technique gained widespread use in adults with acute cardiac dysfunction often secondary to coronary artery disease. However, its use declined after multiple studies failed to show a reduction in mortality and raised concerns of inappropriate use and unnecessary morbidity. In addition, the possibility of "overtreatment" was raised since interventions based on PAC data often did not demonstrate desired clinical benefit. In 2012, the American College of Cardiology Foundation published guidelines on the appropriate use of diagnostic pulmonary artery catheterization in adults. The primary indication is delineation of the presence and magnitude of cardiac dysfunction secondary to suspected acute coronary syndrome.

Due to its technical difficulties and lack of convincing efficacy data in children, the use of the PAC in the pediatric intensive care unit has fallen out of favor. The emergence of novel and less invasive forms of CO determination has further reduced its use. These novel methods include ultrasound-based techniques (e.g., transthoracic echocardiography) and those that utilize transpulmonary thermodilution and pulse contour analysis.

A pulmonary artery catheter should only be placed if a specific question regarding a patient's hemodynamic status cannot be satisfactorily answered by using standard hemodynamic tools and if the answer could impact therapy.

In selected patients, pulmonary artery catheters can be clinically useful allowing for the measurement of the CO, detection of shunts and pulmonary hypertension, and serial monitoring of intracardiac pressures. However, a pulmonary artery catheter should be employed judiciously by a highly experienced physician and for the shortest time period possible.

The interplay of the physiologic variables that a PAC attempts to quantify is valuable from an educational perspective. The appreciation of these interactions allows for a comprehensive understanding of hemodynamics and will be reviewed.

Cardiac Output Determination Using Pulmonary Artery Catheterization

Pulmonary artery catheterization utilizes thermodilution to determine CO. Although only right ventricular output is measured, in the absence of an intracardiac shunt, the right heart CO equals the left heart output. To perform thermodilution CO measurement, a fixed volume of fluid with a known temperature is rapidly injected into the RA via the proximal port of the pulmonary artery catheter. The downstream change in temperature is measured in the pulmonary artery by a thermistor located at the distal end of the catheter. After a thermodilution curve is generated, CO is determined using the Stewart-Hamilton formula.

Accurate CO determination is highly reliant on the area under the curve (AUC) generated during thermodilution. Since the AUC is in the denominator of the Stewart-Hamilton formula, the area under the curve (AUC) is inversely related to CO.

The calculated CO is highly reliant on the area under the curve (AUC) generated during thermodilution. The change in temperature over time determines the AUC. Since the AUC is in the denominator of the equation, the AUC is inversely related to CO. In high CO states, because of rapid mixing and rapid transit of the injectate (cold water), a peak drop in temperature is reached earlier, and the downslope is sharper. This yields a smaller AUC. In low CO states, the transit time diminishes, making the downslope less acute, and therefore the AUC increases (◘ Fig. 16.18). A fundamental assumption is that the fluid injected into the RA will have complete and anatomically appropriate mixing in the RV. Therefore, conditions such as shunts and tricuspid regurgitation can invalidate results.

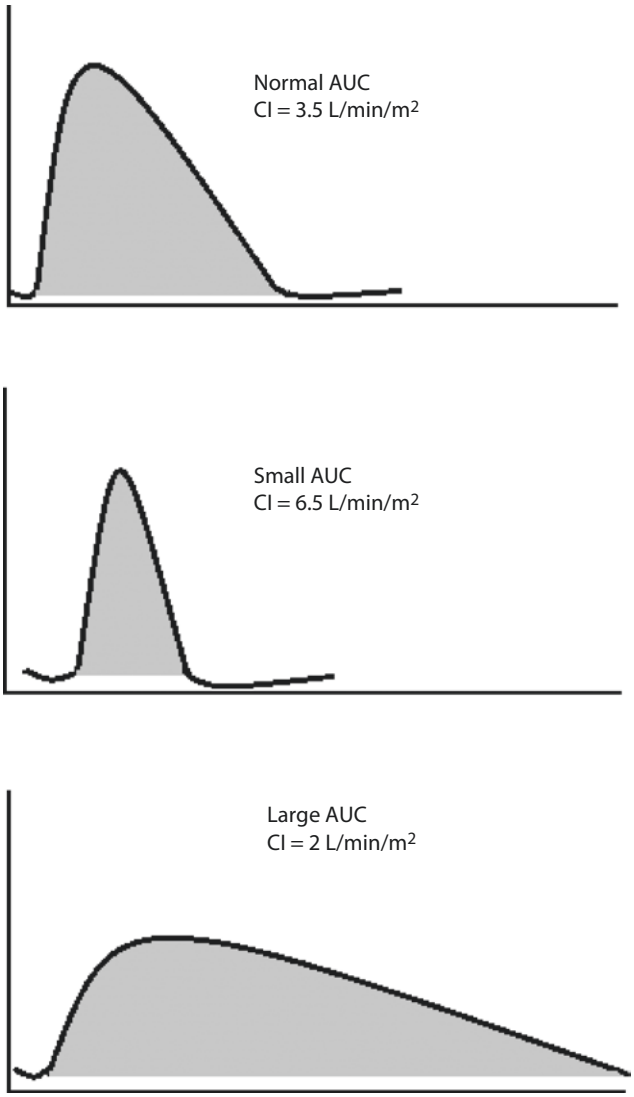


Fig. 16.18 Area under the curve (temperature versus time) and cardiac output relationships

Measuring CO via thermodilution requires expertise and a complete understanding of the technology and the myriad possible analytic errors. Common errors are listed in Table 16.2 and can be summarized as follows: any error leading to a smaller temperature change will decrease the AUC and thus falsely elevate CO, conversely, any error leading to a greater temperature change will increase the AUC and thus falsely lower CO.

When cardiac output is low, more time is required for the blood temperature to return to baseline, producing a larger area under the curve. With high cardiac output, the cooler injectate is carried more quickly through the heart, and the temperature returns to baseline faster. This produces a narrow high peak in the temperature curve with a smaller area under the curve.

Intracardiac Pressure Determination Using Pulmonary Artery Catheterization

Multiple intracardiac pressures can be obtained using a pulmonary artery catheter including right atrial pressure; right ventricular systolic, diastolic, and mean pressures; pulmonary artery systolic, diastolic, and mean pressures; and pulmonary artery occlusion pressure (PAOP) also referred to as the pulmonary capillary "wedge" pressure (Fig. 16.19 and Table 16.3).

The placement of a pulmonary artery catheter allows indirect assessment of left heart pressures. The PAOP is measured at a distal segment of the pulmonary artery and approximates left atrial pressure (LAP). In the absence of

Table 16.2 Potential pitfalls using thermodilution via pulmonary artery catheter to measure cardiac output

Technique error or physiologic anomaly	CO measurement	Explanation
Injectate volume too small	Falsely high CO	Thermistor detects less temperature change and returns to basal temperature sooner, leading to smaller AUC
Injectate volume too large	Falsely low CO	Thermistor detects greater temperature change and returns to basal temperature later, leading to larger AUC
Injectate colder than reference temperature	Falsely low CO	Thermistor detects greater temperature change and returns to basal temperature later, leading to larger AUC
Injectate warmer than reference temperature	Falsely high CO	Thermistor detects less temperature change and returns to basal temperature sooner, leading to smaller AUC
Injection rate too slow	Falsely high CO	Blood remains warm during slow injection. Thermistor detects return to basal temperature sooner, leading to smaller AUC
Tricuspid regurgitation	Falsely low CO[a]	Cold injectate is recycled from RV to RA leading to delayed downstream (PA) temperature change. Thermistor detects return to basal temperature later, leading to larger AUC
Right to left shunt	Falsely high CO	Premature loss of indicator across shunt. Thermistor detects return to basal temperature sooner, leading to smaller AUC
Left to right shunt	Falsely low CO	Cold injectate recycled back to right heart. Thermistor detects return to basal temperature later, leading to larger AUC

[a]Tricuspid regurgitation has also been reported to falsely elevate CO. Cold injectate is warmed as it contacts greater surface area of endocardium. Therefore, thermistor detects return to basal temperature sooner, leading to smaller AUC and falsely high CO

16

significant mitral valve disease, LAP approximates left ventricular end-diastolic pressure (LVEDP). If the PAOP and pulmonary artery end-diastolic pressure correlate well, the pulmonary artery diastolic pressure (PADP) can likewise be used as an indirect assessment of LVEDP. LVEDP is generally reduced with low preload or increased with poor LV compliance. Typically, the mean value of the PAOP is similar to the PADP. Therefore, in ideal physiological conditions:

PAOP approximates LAP, which in turn reflects LVEDP. If the PADP correlates with the PAOP, the PADP can be used to approximate LAP.

Pulmonary artery occlusion pressure approximates left atrial pressure which reflects left ventricular end-diastolic pressure (LVEDP). LVEDP is generally reduced with low preload or increased with poor LV compliance.

It is important that the catheter tip is in a branch of the pulmonary artery that is least affected by alveolar pressure. This condition is met near the base of the lung, West Zone 3, where $P_{art} > P_{vein} > P_{alv}$ (Fig. 16.20). Zone 3 provides a continuous column of blood from the balloon tip to the pulmonary vein and is least affected by alveolar pressure.

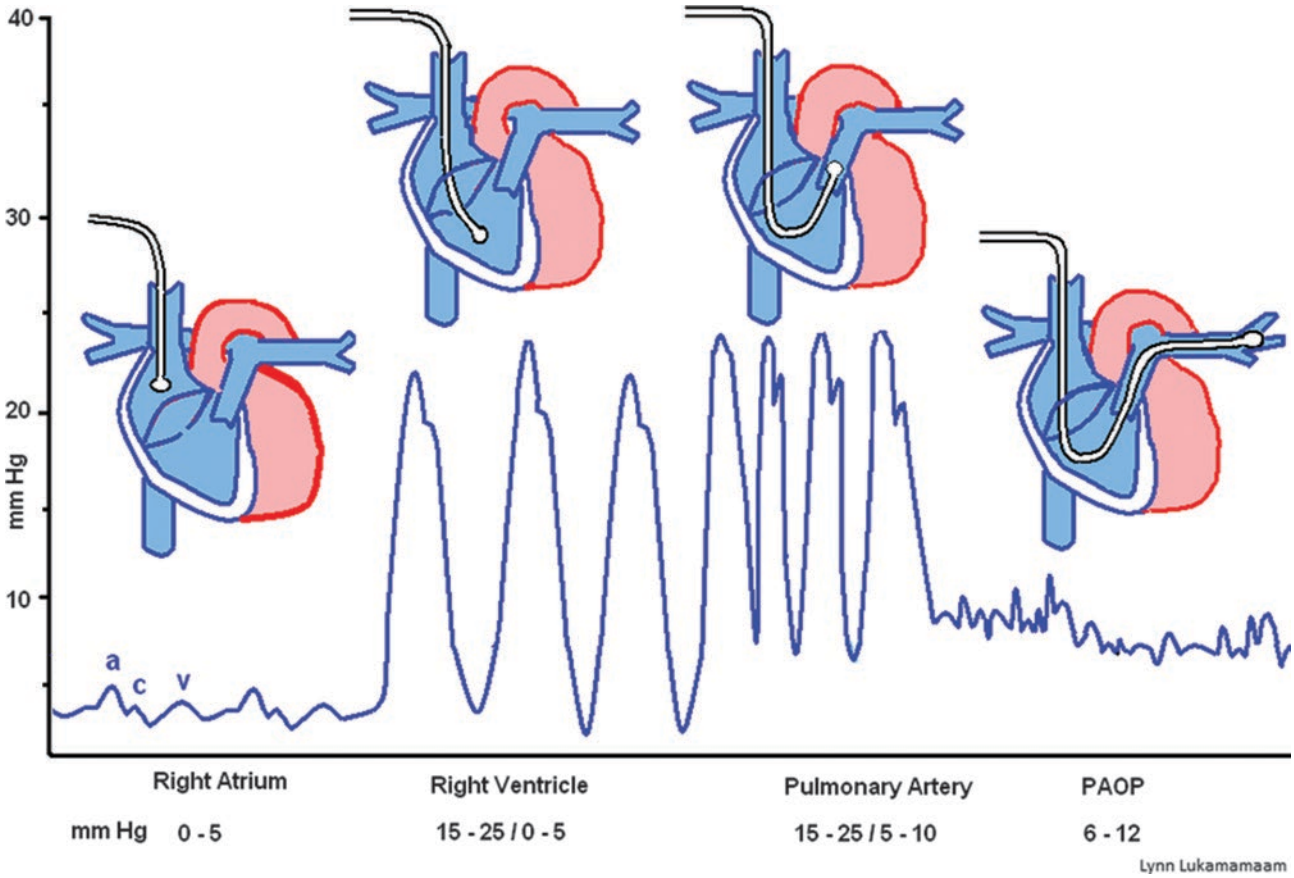


Fig. 16.19 Right heart pressure waveforms and normal values as obtained by pulmonary artery catheterization

Table 16.3 Normal ranges for intracardiac pressures and oxygen saturations

Parameter	Normal pressure range (mm Hg)	Normal oxygen saturation range
Right atrial pressure	0–6	65–80%[a]
Right ventricle systolic/diastolic	15–25/0–10	70–75%
Pulmonary artery systolic/diastolic	15–25/5–10	70–75%
Pulmonary wedge pressure	6–12	N/A
Left atrium	4–12	100%
Left ventricle	60–90[b]/4–12	100%

[a]Oxygen saturations in the central veins or right atrium should be measured using co-oximetry and interpreted according to the exact sampling site. With stable hemodynamics, superior vena cava oxygen saturations are generally lower than inferior vena cave saturations due to greater cerebral oxygen extraction. Catheters placed deep in the right atrium may have lower saturations due to coronary sinus blood sampling, which is normally markedly desaturated

[b]Ventricular pressures are age dependent and increase from infancy to older children

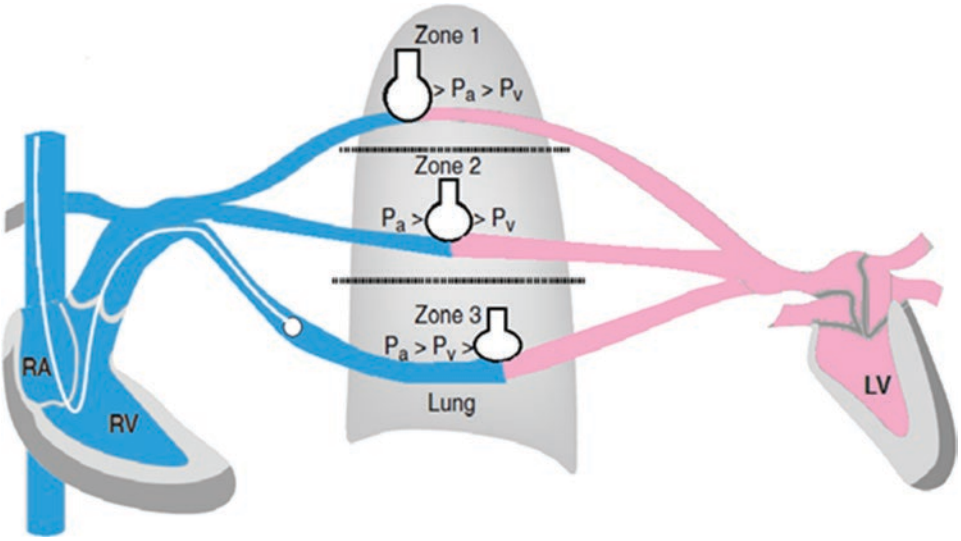


Fig. 16.20 West zones and the relationship of alveolar, pulmonary artery, and pulmonary vein pressures. *Zone 1*, $P_{Alveoli} > P_{artery} > P_{vein}$; *Zone 2*, $P_{artery} > P_{Alveoli} > P_{vein}$; and *Zone 3*, $P_{artery} > P_{vein} > P_{Alveoli}$. The PAC should ideally wedge into a branch of the pulmonary vasculature contributing to West Zone 3 of the lung. P_A, alveolar pressure; P_a, arteriolar pressure; P_V, pulmonary venous pressure; P Art, pulmonary artery; P Veins, pulmonary veins; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle

The tip of the PAC during PAOP measurement should be in Zone 3 near the base of the lung, where $P_{art} > P_{vein} > P_{alv}$.

Obtaining and Interpreting Pulmonary Artery Occlusion Pressures

When utilizing a pulmonary artery catheter, PAOP measurement is a proxy for left heart hemodynamics. A small balloon located at the tip of the pulmonary artery catheter facilitates the measurement of PAOP. The balloon is inflated and "floated" into a distal branch of the pulmonary artery where it becomes "wedged." With the balloon inflated, flow in the distal segment of the pulmonary artery is occluded creating a continuous uninterrupted column of blood from the tip of the pulmonary artery catheter to the left atrium. Once wedged, the waveform changes from a pulmonary artery waveform to an atrial waveform with characteristic ***a*** and ***v*** waves. Once the PAOP measurement is obtained, the balloon should be deflated to avoid distal pulmonary artery injury.

Abnormal PAOP values should be assessed concomitantly with stroke volume index (SVI). An elevated PAOP (>18 mm Hg) and low SVI are consistent with poor LV compliance and reduced contractility. A low PAOP < 6 mm Hg in the context of a low SVI is consistent with decreased LV preload.

A normal PAOP is 6–12 mm Hg. An abnormally high or low PAOP value should be assessed in the context of myocardial performance, which is best reflected by the stroke volume index (SVI, which is SV/body surface area). An elevated PAOP (>18 mm Hg) and decreased SVI suggest poor LV compliance and reduced contractility. Conditions such as congestive heart failure, myocardial infarction, cardiac tamponade, and cardiomyopathy are associated with a high PAOP and low SVI. In these circumstances, titrating fluid management to PAOP may help avoid worsening cardiogenic pulmonary edema. A low PAOP <6 mm Hg and decreased SVI are consistent with decreased LV preload that may occur in conditions such as dehydration, hemorrhage, and loss of effective circulating volume (e.g., third spacing of vascular fluid from capillary leak).

The interpretation of PAOP and its relationship to LVEDP requires an appreciation of possible coexisting pathologies and technical limitations (Box 16.4). Valvular disease, in particular, affects the ability of PAOP to accurately reflect LVEDP. PAOP will overestimate the LVEDP in mitral valve disease such as mitral stenosis. The high LAP (and therefore PAOP) associated with mitral stenosis does not reflect the end-diastolic volume or compliance of the LV.

The PAOP may at times not be reflective of the true LVEDP during states of increased pulmonary vascular resistance as the fluid column transmits the high pressure from the vascular bed and not the left heart. Aortic regurgitation causes PAOP to underestimate the true LVEDP. During aortic regurgitation, the mitral valve closes prematurely as retrograde aortic flow continues to fill the LV and add to LVEDP.

PAOP will also underestimate LVEDP in the setting of poor left ventricular compliance. Atrial contraction into a stiff ventricle produces a rapid rise in LVEDP that causes premature closure of the mitral valve. Therefore, the LA and PAOP will be "protected" from transmission of high LVEDP; however, a prominent ***a*** wave will be appreciated as the LA contracts against a poorly compliant LV. In this setting, measuring the ***a*** wave of the PAOP rather than the mean PAOP may be more reflective of LVEDP.

Box 16.4 Conditions Resulting in Discrepant PAOP and LVEDP Measurements

PAOP overestimates LVEDP

- Excessive positive mean airway pressure
- Placement of catheter in West Zone I or II
- Mitral valve disease
- Increased pulmonary vascular resistance
- Atrial myxoma

PAOP underestimates LVEDP

- Aortic regurgitation
- Low LV compliance

Pulmonary Artery Diastolic Pressure (PADP)

The PADP is sometimes used in place of the PAOP to assess LVEDP. The pulmonary artery waveform is characterized by a rapid upstroke and a rounded peak followed by a rapid downstroke as right ventricular blood is ejected into the pulmonary artery. Similar to the aortic arterial waveform, a notch is observed on the downslope and is caused by the closure of the pulmonic valve (recall that the closure of the aortic valve causes the incisura present on the aortic waveform). The waveform pressure falls off progressively during diastole. To identify pulmonary artery peak systolic and end-diastolic pressures, the corresponding ECG tracing should be examined; end-diastole occurs at the end of the QRS complex and peak systole occurs within the T wave.

It is technically easier and safer to measure PADP rather than performing repetitive wedging to obtain serial PAOPs. In addition to PAOP limitations previously described, PADP may be altered by other pathologies. Pulmonic valve regurgitation causes PADP to underestimate LVEDP because of bidirectional runoff of pulmonary artery blood during diastole. Tachycardia can also cause PADP to overestimate the LVEDP. Tachycardia causes a shorter diastole so there is less time for blood to flow from the pulmonary veins to left heart, and therefore, the pressure gradients do not have time to equilibrate and PADP will increase. Consequently, tachycardia-induced increase in PADP overestimates LVEDP.

Derived Hemodynamic Variables

In addition to monitoring intracardiac pressures and CO determination, data obtained from a pulmonary artery catheter provides variables for multiple hemodynamic calculations such as systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR), which are typically normalized to BSA (SVRI and PVRI). Because of the multiple factors that affect afterload, true afterload cannot be measured using a pulmonary artery catheter. However, systemic and pulmonary vascular resistance, a component of LV and RV afterload, respectively, can be calculated using a pulmonary artery catheter.

Table 16.4 Derived hemodynamic calculations

Variable	Formula	Normal range
Cardiac index (CI)	CO/BSA[a]	3.0–5.5 L/min/m^2
Stroke volume (SV)	CO/HR	60–100 mL/beat
Stroke volume index (SVI)	CI/HR or SV/BSA	30–60 mL/beat/m^2
Systemic vascular resistance index (SVRI)[b, c]	MAP – RAP/CI × 80	800–1600 dyne-s/cm^5/m^2
Pulmonary vascular resistance index (PVRI)[b, c]	MPAP – PAOP/CI × 80	80–200 dyne-s/cm^5/m^2
Arterial oxygen content (CaO_2)	Hgb × 1.34 mL O_2/g Hgb × SaO_2 + (.003 × PaO_2)	17–20 mL/dL
Mixed venous oxygen content ($CmvO_2$)	Hgb × 1.34 mL O_2/g Hgb × SvO_2 + (.003 × PvO_2)	12–15 mL/dL
Oxygen delivery index (DO_2I)[d]	CaO_2 × CI × 10	550–680 mL/min/m^2
Arterial-mixed venous oxygen difference (a-vDO_2)	CaO_2 – CvO_2	3–5 mL/dL or 30–50 mL/L
Oxygen extraction ratio (O_2ER)	(CaO_2 – CvO_2)/CaO_2 or (SaO_2 – SvO_2)/SaO_2 or VO_2/DO_2	0.24–0.28
Oxygen consumption index (VO_2I)[d]	(CaO_2 – $CmvO_2$) × CI × 10	120–200 mL/min/m^2

[a]Cardiac output in relation to body size is high in the neonatal period. The cardiac index of a newborn slowly diminishes to adult values (3.0–4.0 L/min/m^2) by early adolescence

[b]Both SVR and PVR are typically indexed to body surface area (SVRI and PVRI). The ranges of normal values for SVRI and PVRI vary accordingly based on the child's body surface area and age. By normalizing the calculation using CI rather than CO, the variation by age is less with PVRI and SVRI compared with PVR and SVR

[c]To convert dyne-s/cm^5 to Wood units, divide by a factor of 80. The normal range of SVRI is approximately 10–20 Wood units/m^2 and PVRI is approximately <1–3 Wood units/m^2

[d]Since CI is measured in L/min and oxygen content is measured in ml/100 mL of blood, the formula includes multiplication by "10" to convert the oxygen content to ml/L of blood

The quantification of SVRI can aid in tailoring inotropic, pressor, and vasodilator therapy. Similarly, therapies directed at treating pulmonary hypertension (e.g., hyperoxia, alkalosis, nitric oxide, etc.) can be monitored with continuous PVRI data. Hemodynamic parameters that can be calculated during pulmonary artery catheterization are summarized in Table 16.4.

The potential complications of pulmonary artery catheter placement are numerous and include life-threatening arrhythmias and pulmonary artery or intracardiac injury. Complications may occur during insertion and manipulation or be related to maintenance of the pulmonary artery catheter (Box 16.5). Although not a true complication, a potential risk in using the PAC for decision making is the use of erroneous data or overestimating the clinical significance of appropriately obtained data.

Box 16.5 Complications Related to Pulmonary Artery Catheter Insertion and Use

Pulmonary artery catheter complications
Arrhythmias
Heart block
Inability to withdraw catheter due to knotting
Valve injury
Endocardial injury
Pulmonary infarction
Endocarditis
Pulmonary artery rupture
Pulmonary artery pseudoaneurysm
Misinterpretation of the data

16.2.4 Novel Techniques for Cardiac Output Assessment

16.2.4.1 Pulse Contour Analysis

Pulse contour analysis is based on the principle that the area under the curve (AUC) of the systolic portion of an arterial waveform correlates with the stroke volume. The estimation of the stroke volume from pulse contour analysis during heart rate monitoring allows for beat-to-beat CO assessment. A limitation of this technology involves the contribution of arterial compliance to the arterial pulse waveform. Recall that the arterial waveform is produced by LV ejection stroke volume *and* the pulsatile waves reflecting back from arterial walls. The reflection of pulse waves off arterial walls is dependent upon the compliance characteristics of the arterial tree. The aortic and arterial compliance is highly variable between individuals and during disease states. The compliance of the aorta and the distal arteries impacts the shape of the waveform with less compliant arteries causing an increase in the systolic peak. Due to the dynamic nature of arterial compli-

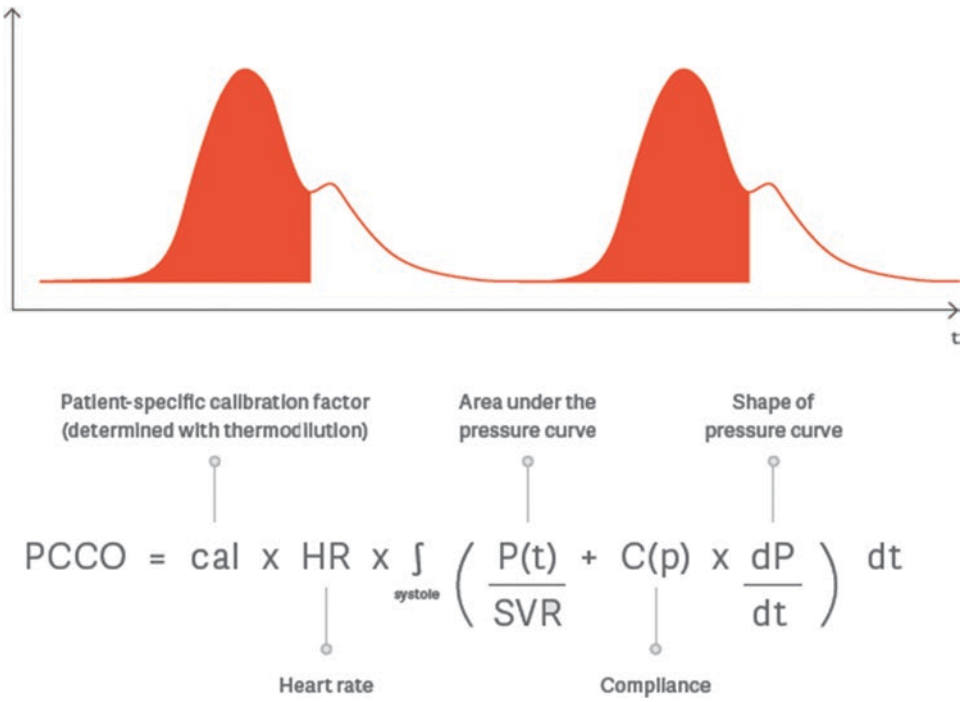


Fig. 16.21 Graphical and mathematical display of improved pulse contour algorithm for determination of cardiac output. Pulsion Medical Systems

ance, the use of pulse contour analysis requires serial calibration with another method of CO determination. Serial calibration is especially important in the critically ill patient due to patient-specific differences in the arterial physical properties, changes in the vascular tone, and varied volume status.

There are two methods for calibration that are currently in use. The pulse-induced contour cardiac output (PiCCO) system uses the transpulmonary thermodilution method to calibrate CO with pulse contour analysis. Transpulmonary thermodilution (TPTd) uses the principle of thermodilution to determine CO but measures temperature changes in a central artery (usually the femoral) following an injection of a cold saline bolus into a central vein with the injectate traversing the pulmonary circulation. Multiple studies found the PiCCO system to correlate well with values obtained using the direct Fick and pulmonary artery catheter-based thermodilution methods. The mathematic algorithm used to determine beat-to-beat CO has undergone refinements that have added to its reliability (◘ Fig. 16.21). In addition, preload can be measured periodically along with intrathoracic blood volume (ITBV), global EDV (GEDV), and extravascular lung water (EVLW).

The lithium dilution cardiac output (LiDCO™) system uses a lithium calibration technique. With lithium cardiac output determination, instead of temperature change over time producing an AUC, the change in lithium concentration over time produces an AUC that is used to compute CO. During calibration, a small known dose of lithium is injected into a vein. In a peripheral artery, an ion-selective electrode sensor plots the concentration of lithium over time to calculate the CO. Once a calibration factor is determined, the system calculates CO using a proprietary algorithm that converts an arterial blood pressure waveform-based signal into an arterial blood flow measurement. A limitation of this technique is the need for lithium injection, which is less safe and more costly than saline injection.

Other systems (e.g., Flo Trac/Vigileo, LiDCOrapid) do not use a second method for CO determination for calibration. In contrast to the PiCCO and LiDCO, these systems use algorithms that integrate physiologic assumptions based on the patient's demographic and physical characteristics to predict stroke volume. These physiologic assumptions include compliance and systemic vascular resistance.

Both the calibrated and non-calibrated systems continue to undergo validation studies to assess their ability to estimate CO in different clinical conditions. Studies have demonstrated that during hemodynamic instability, measured CO based on continuous arterial pulse contour analysis shows only limited agreement with PAC-based thermodilution. The calibrated systems may provide more accurate measurements than the non-calibrated systems. Limited data exist in children; however, pulse contour analysis has shown poor agreement with PAC-based cardiac output determination in children with congenital heart disease, pulmonary hypertension, and cardiomyopathy. Currently, both calibrated and non-calibrated pulse contour technologies are not recommended for routine use in the pediatric intensive care unit.

Pulse contour waveform analysis evaluates the AUC of the systolic portion of the arterial waveform and equates it to stroke volume. The estimation of the stroke volume from pulse contour analysis during heart rate monitoring allows for beat-to-beat CO assessment. The compliance of the arterial tree must be considered when using pulse contour analysis.

Due to the dynamic nature of arterial compliance, the use of pulse contour analysis requires serial calibration with another method of CO determination such as transpulmonary thermodilution.

16.2.4.2 Transesophageal Doppler Echocardiography

Cardiac echocardiography is a proven tool in the evaluation of cardiac anatomy and function in critically ill children. Transesophageal Doppler echocardiography (TDE) measures aortic flow velocity via a carefully positioned Doppler probe. Cardiac output can then be calculated by the product of the aortic velocity time integral (VTI), the cross-sectional area (CSA) of the aorta, and the heart rate:

$$\text{CO} = \text{Aortic CSA cm}^2 \times \text{VTI} \times \text{heart rate}$$

These measurements require optimal positioning of the probe and precise timing during systole when flow is measured. The technique requires specialized training and equipment. Although studies in children have found good correlation between TDE and thermodilution, the technique is highly dependent upon proper positioning of the probe with overestimation and underestimation of CO not uncommon. The value of TDE may be limited in clinical practice due to the need for precise probe placement, lack of continuous data, need for sedation during probe placement, and operator variability.

16.2.4.3 Inadequate Oxygen Delivery Index (IDO_2)

At every critical care bedside, a plethora of real-time continuous physiologic data is being recorded. The ability to integrate and analyze meaningful portions of this data to improve outcomes is increasingly challenging. Clinical support algorithms based on reliable continuous data are being developed to identify adverse clinical trends that may lead to poor outcomes.

An example of software that analyzes continuous physiologic data is data aggregation and visualization software (Etiometry, Inc., Boston, MA) which is FDA cleared for use in critically ill children. The software collects, visualizes, and stores PICU data in near real time and provides a patient-specific risk of inadequate delivery of oxygen (IDO_2). Ten physiologic values from the bedside monitor and standard laboratory values are inputted into an algorithm, and an IDO_2 index is computed in real time. The index is calculated at 5 s intervals and provides the probability (between 0 and 100) of the measured mixed systemic venous saturation being less than 40%. Therefore, an increasing IDO_2 index value may identify children at increased risk of inadequate oxygen delivery and tissue hypoxia.

Although the technology appears promising, early study results are mixed. A retrospective cohort study demonstrated that an increasing IDO_2 in neonates who were post-operative from congenital heart disease repair was associated with an increased risk of cardiac arrest. However, a retrospective study comparing a modified low cardiac output syndrome score (LCOSS) and the IDO_2 found the LCOSS had a stronger association with postoperative adverse events. The LCOSS uses postoperative tachycardia, low urine output (<1 mL/kg/h), low temperature (<30 °C), raised inotropic requirement, increased volume administration (>30 mL/kg/d), decreased NIRS measurement (cerebral and renal NIRS <50% and 75% of arterial saturations, respectively), and elevated arterial lactate (>2 mmol/L) as markers of deterioration. The brain and myocardium are high extractors, consuming 35–40% and 50–65% of oxygen delivered respectively, whereas the skin and kidney are low extractors.

16.2.5 Cardiac Biomarkers

16.2.5.1 Mixed Venous and Central Venous Oxygen Saturation

At rest, the body normally extracts only 25% of the total amount of oxygen delivered. This can be remembered by recalling that each hemoglobin molecule carries four oxygen molecules, one of which is normally consumed during transit from the arterial to venous circulation. Provided that cardiac output is adequate to meet tissue oxygen demand and the hemoglobin concentration is in the normal range, only approximately 25% of the delivered oxygen is consumed.

In a healthy steady state, DO_2 is luxurious when compared to oxygen demand with approximately 75% of the oxygen delivered remaining unused. Oxygen extraction varies across organ beds. The brain and myocardium are high extractors, consuming 35–40% and 50–65% of oxygen delivered respectively, whereas the skin and kidney are low extractors. A true mixed venous

Provided that cardiac output is adequate to meet tissue oxygen demand and the hemoglobin concentration is in the normal range, only approximately 25% of the delivered oxygen is consumed.

Oxygen extraction varies across organ beds. The brain and myocardium are high extractors, consuming 35–40% and 50–65% of oxygen delivered respectively, whereas the skin and kidney are low extractors.

saturation ($SmvO_2$) allows for a global assessment of the body's oxygen extraction. The measurement must occur after venous return from all organ beds is "mixed" to avoid having the $SmvO_2$ reflect a single organ bed's oxygen extraction. Using a pulmonary artery catheter, the $SmvO_2$ is obtained in the pulmonary artery. Without a pulmonary artery catheter in place, the pulmonary artery $SmvO_2$ can be closely approximated by sampling venous blood from a central catheter with its tip at the SVC-RA junction. When a venous blood oxygen saturation is determined from the SVC-RA junction or other central site, it is referred to as a central venous oxygen saturation ($ScvO_2$) or right atrial saturation. Since venous oxygen saturation is on the steep portion of the oxyhemoglobin dissociation curve, it is essential that the oxygen saturation is measured using co-oximetry rather than the calculated oxygen saturation from a standard or bedside blood gas machine since critical illness can alter the normal dissociation curve.

Central venous oxygen saturation values below 60% indicate increased oxygen extraction by the tissues. This may be due to either a decrease in oxygen delivery or an increase in tissue oxygen demands.

The normal oxygen saturation of central venous blood returning to the right heart ($ScvO_2$) is between 65% and 75%, assuming normal arterial oxygen saturation. Central venous oxygen saturation values below 60% indicate increased oxygen extraction by the tissues. This may be due to either a decrease in oxygen delivery or an increase in tissue oxygen demands. Common causes of decreased oxygen delivery include reduced cardiac output, anemia, and/or low arterial oxygen saturation (hypoxemia). Alternatively, a low $ScvO_2$ may reflect increased tissue oxygen demands such as due to increased work of breathing, fever (oxygen consumption increases by ~10% per degree increase in temperature), seizures, shivering, pain, physical activity, or catheter migration near or into the coronary sinus. Low $ScvO_2$ values below 60% are often accompanied by acidosis due to a shift to anaerobic metabolism (see lactate below). A normal or high $ScvO_2$ may also be associated with tissue hypoxia. An elevated $ScvO_2$ may occur with appropriate or even supranormal DO_2 in the setting of impaired cellular and/or mitochondrial oxygen uptake (e.g., cyanide toxicity). In addition, the ScvO2 may be preserved if microcirculatory shunting results in excess blood flow to some tissue beds while other regions remain ischemic. This microcirculatory shunting may be observed in the setting of severe vasodilatory sepsis.

ScvO2 may vary based on catheter position, disease state, and even age of the child. In the healthy state, the superior vena cava (SVC) has a slightly lower venous oxygen saturation than the inferior vena cava (IVC) in part due to high cerebral oxygen extraction and low renal oxygen extraction.

It is important to note that, although a good surrogate for $SmvO_2$, $ScvO_2$ may vary based on catheter position, disease state, and even age of the child. In the healthy state, the superior vena cava (SVC) has a slightly lower venous saturation than the inferior vena cava (IVC) in part due to high cerebral oxygen extraction and low renal oxygen extraction. This is especially true in small children where the relatively large growing brain is a major oxygen extractor. Therefore, the $SmvO_2$ is greater than $ScvO_2$ by about 2–3%. The relationship between the SVC and IVC saturation may reverse in the setting of shock (Fig. 16.22). In adults with cardiogenic or hypovolemic shock, mesenteric and renal blood flow decreases, and oxygen extraction increases causing the IVC saturation to become lower than the SVC. Therefore, during certain shock states, the $ScvO_2$ may become greater than $SmvO_2$. Despite these differences, most authors believe that changes in $ScvO_2$ closely reflect changes in $SmvO_2$ and therefore remain a good marker of oxygen delivery and extraction.

In summary, a decreased $ScvO_2$ is associated with decrements in cardiac output, hemoglobin concentration, and/or arterial oxygen saturation, and it varies inversely with oxygen consumption. It is an extremely useful marker for tissue hypoperfusion. Measurements can be followed serially, or continuously using a fiber-optic central venous catheter, to assess the impact of therapeutic maneuvers such as fluid resuscitation, blood transfusion, and inotropic support (Table 16.5). Achievement of $ScvO_2 \geq 70\%$ is a therapeutic endpoint in the resuscitation from sepsis and septic shock as articulated in the Surviving Sepsis Campaign sponsored by the Society of Critical Care Medicine.

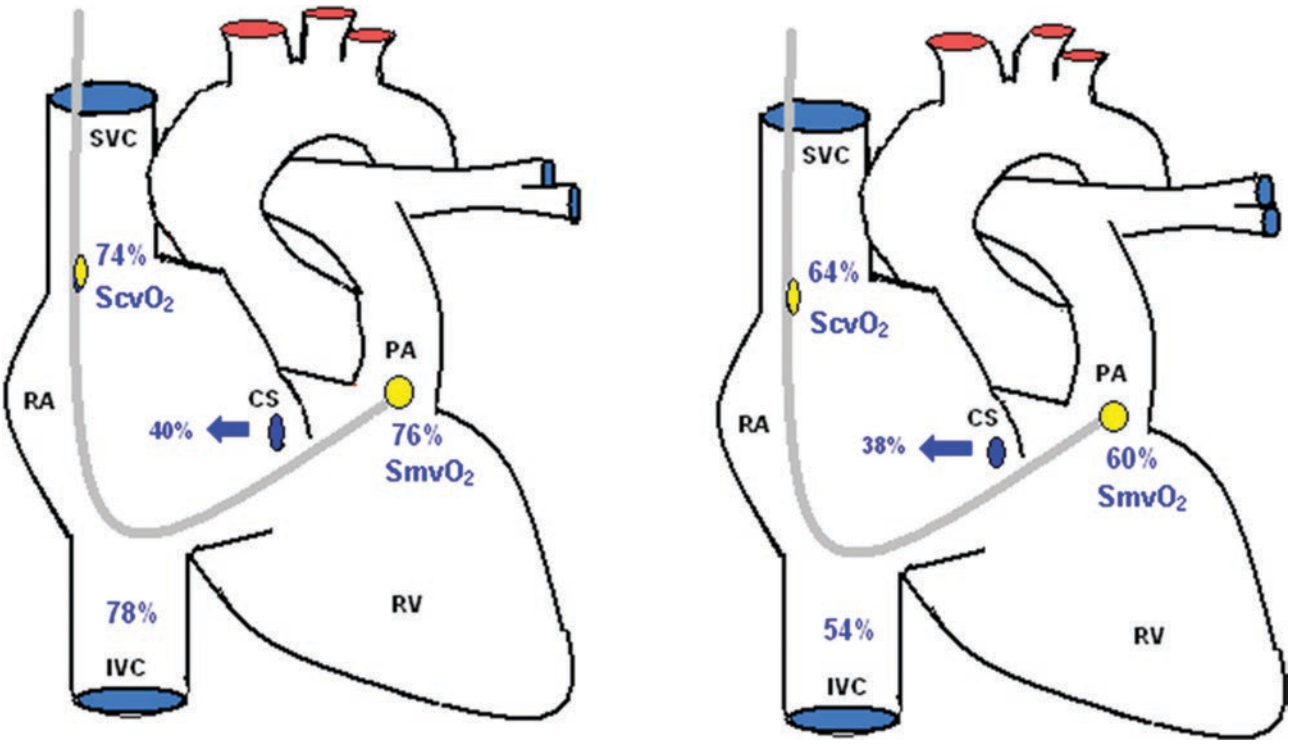


Fig. 16.22 Relationship between central venous oxygen saturation ($ScvO_2$) and mixed venous saturation ($SmvO_2$) during health (left) and cardiogenic or hypovolemic shock (right). Normally, the $SmvO_2$ will be slightly higher than the $ScvO_2$, whereas shock states may produce a reversal of this relationship. SVC superior vena cava, IVC inferior vena cava, RA right atrium, CS coronary sinus, RV right ventricle

Table 16.5 Troubleshooting abnormalities in mixed or central venous oxygen saturations

Low $ScvO_2$	High $ScvO_2$
Anemia	High cardiac output states
Low cardiac output states	Defect in oxygen extraction
Hypoxemia	Decreased metabolic rate
Increased metabolic rate	Supranormal oxygen delivery

16.2.5.2 Lactate

Lactate metabolism is complex, and its production is highly dependent upon the physiological milieu at the cellular level. Although lactic acidosis is often used as a marker of cellular hypoxia, lactate may be elevated in non-hypoxemic environments without accompanying metabolic acidosis. It is important to recognize that the laboratory measures only the lactate anion; thus, an increased lactate concentration may not always be accompanied by metabolic acidosis.

A biochemical review of lactate production is helpful in understanding hyperlactatemia during critical illness. Cellular respiration is the process by which glucose is utilized to produce cellular energy in the form of adenosine triphosphate (ATP) (Fig. 16.23). The cytosolic component of the process does not require oxygen and consists of glycolysis, whereas the mitochondrial portion is highly dependent on oxygen and consists of the tricarboxylic acid

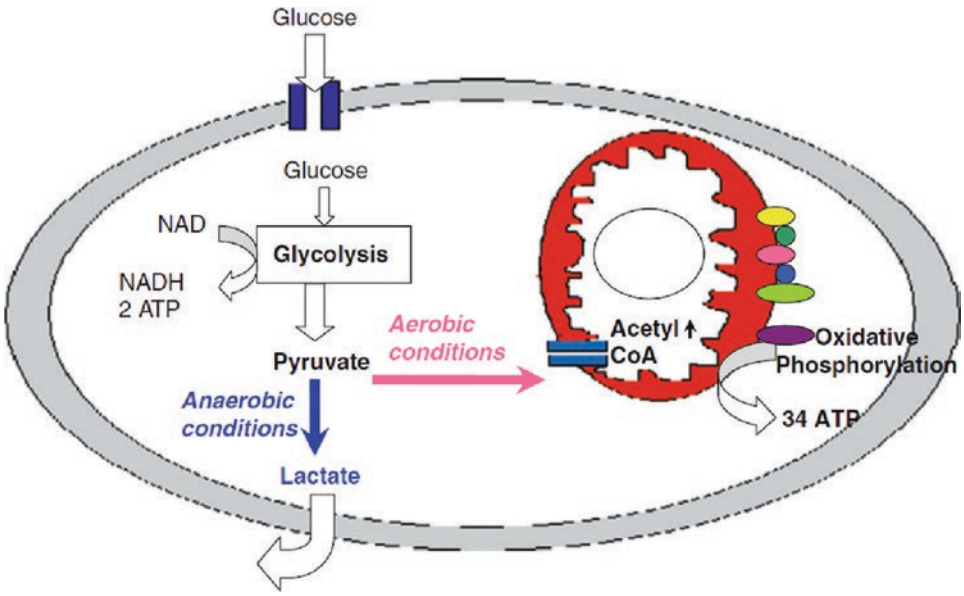


Fig. 16.23 Overview of cellular respiration and lactate production

(TCA) cycle (also known as citric acid cycle or Krebs cycle) and oxidative phosphorylation (also referred to as mitochondrial membrane electron transport). During glycolysis, glucose is converted to pyruvate with the net production of 2 molecules of ATP. Most of the energy production from glucose metabolism occurs in the mitochondria during the tricarboxylic acid cycle (2 ATP) and oxidative phosphorylation (32 ATP). A small amount of lactate is normally produced during glycolysis, but it is rapidly metabolized by the liver and excreted by the kidney. Thus, normal serum lactate levels remain less than 2 mmol/L.

During hypoxia, shunting of pyruvate towards anaerobic metabolism results in an elevated plasma lactate and an elevation in the lactate-to-pyruvate ratio (normal 10:1). Elevated lactate in the setting of acidosis has been used as a marker of tissue hypoperfusion.

Lactate production is increased dramatically during hypoxia. Due to low intracellular oxygen tension, pyruvate can no longer undergo aerobic metabolism in the mitochondria and is shunted toward lactate production. Hypoxia is also known to decrease the activity of pyruvate dehydrogenase, which converts pyruvate to acetyl-CoA. The continued shunting of pyruvate toward lactate production results in an elevated plasma lactate and an elevation in the lactate-to-pyruvate ratio (normal 10:1).

Lactic acidosis due to hypoperfusion has been traditionally referred to as type A lactic acidosis and is associated with an elevated lactate-to-pyruvate ratio. Elevated lactate in the setting of acidosis has been used as a marker of tissue hypoperfusion and anaerobic metabolism. Multiple studies have correlated rising lactate levels and mortality in patients with a variety of critical illnesses. However, studies utilizing lactate as a resuscitation endpoint to improve survival have been inconclusive.

Hyperlactatemia in critical illness may not be solely due to cellular hypoxia. Non-hypoxemic (type B lactic acidosis) elevations of serum lactate may occur during normal perfusion or after hypoperfusion has been corrected.

Hyperlactatemia in critical illness may not be solely due to cellular hypoxia. Non-hypoxemic (type B lactic acidosis) elevations of serum lactate may occur during normal perfusion or after hypoperfusion has been corrected. Lactate production may be increased during states of "hyperglycolysis." Excessive catecholamine states have been found to stimulate glycolysis at a rate that exceeds the oxidative capacity of the mitochondria and lead to type B lactic acidosis. Increased skeletal muscle and hepatic glycolysis results in increases in both pyruvate and lactate production, thus maintaining the lactate-to-pyruvate ratio. The resultant increased pyruvate is then metabolized to lactate at a much higher than normal rate. Hyperadrenergic states are common in the

pediatric ICU and include exogenous administration of catecholamines and disorders associated with a vigorous systemic inflammatory response (e.g., acute lung injury, trauma, sepsis, burns). Type A or type B lactic acidosis may be further accentuated in the setting of decreased hepatic metabolism and/or renal clearance.

Hyperlactatemia may also occur due to drug or toxin effects. Any drug that interferes with the TCA cycle or oxidative phosphorylation may lead to excessive lactate production. These medications include metformin, salicylates, HMG CoA reductase inhibitors, cyanide, iron, and propofol. Inborn errors of metabolism may also present with profound elevations in serum lactate concentration. Examples of inborn errors of metabolism that may present with lactic acidosis include pyruvate dehydrogenase deficiency, pyruvate decarboxylase deficiency, glucose-6-phosphatase deficiency, fructose-1,6-diphosphatase deficiency, and mitochondrial disorders. In addition, certain malignancies may be associated with hyperlactatemia. Finally, hyperlactatemia may be caused by elevation in the D-isomer of lactate. This is usually observed in states of intestinal bacterial overgrowth as occurs in short gut syndrome.

Studies have shown an association between persistently elevated plasma lactate levels and mortality in critically ill children and neonates. The ability of a single admission or first postoperative lactate level to predict adverse outcomes is poor. However, like many biomarkers, lactate is best used as trended data. Persistently elevated lactate levels 6–12 h after cardiac surgery have been associated with an increased risk of major adverse events.

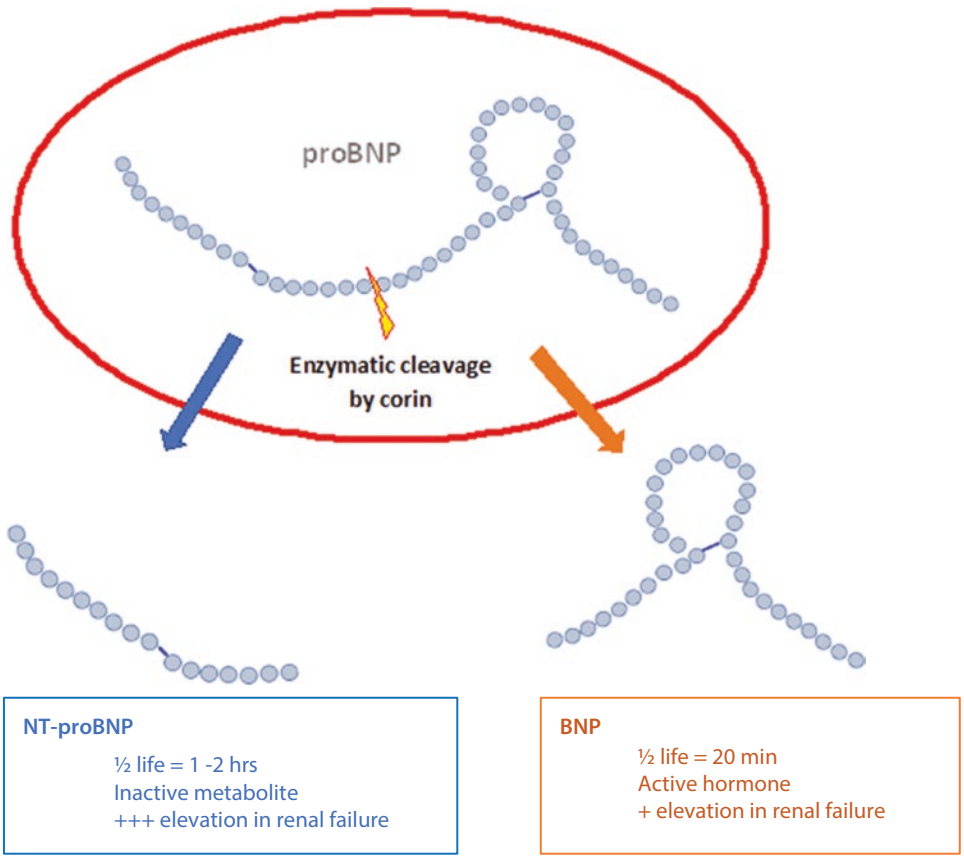


Fig. 16.24 Overview of proBNP metabolism and comparison between NT-proBNP and BNP

16.2.5.3 B-Type Natriuretic Peptide

B-type natriuretic peptide, initially isolated in porcine brains, was previously referred to as brain natriuretic peptide. The peptide was later found to be produced mainly by ventricular myocytes, leading to its more appropriate name – B-type natriuretic peptide (BNP). ProBNP is enzymatically cleaved to N-terminal proBNP (NT-proBNP) and the physiologically active BNP (Fig. 16.24). BNP synthesis occurs in response to increased ventricular wall stress caused by volume or pressure overload.

BNP has several physiologic effects that contribute to cardiovascular compensation in the setting of heart failure. The peptide increases cGMP in vascular smooth muscle resulting in vasodilation, venodilation, and afterload reduction. BNP suppresses the renin-angiotensin-aldosterone system, thus promoting diuresis and natriuresis. In addition, BNP may have a beneficial role in the prevention of pathologic myocardial remodeling that may occur in advanced heart failure.

Both BNP and NT-proBNP can be easily measured in whole blood. Assays for NT-proBNP likely measure a mixture of NT-proBNP and proBNP. The advantage of measuring NT-proBNP versus BNP is its longer half-life (1–2 h versus 20 min) and longer stability at room temperature (72 h versus 24 h). Variability in assays must be considered when interpreting serial BNP or NT-proBNP results. Biologic variation also occurs among individuals based on age, sex, and body mass.

Multiple adult studies confirmed the utility of both markers in ruling out heart failure and to gauge therapeutic response. Using a cutoff of 100 pg/ml, the BNP assay has a clinical specificity for heart failure of >96%. The ability to rule in heart failure (sensitivity) is lower. Data in children suggest the markers can aid in the diagnosis and management of a variety of pediatric cardiovascular diseases (e.g., congenital heart defects, cardiomyopathy, and pulmonary hypertension). Normal pediatric values are BNP of less than 25 pg/ml and a NT-proBNP level less than 70 pg/ml. Levels of both peptides are higher in newborns but normalize by the second week of postnatal life.

16.2.5.4 Cardiac Troponin

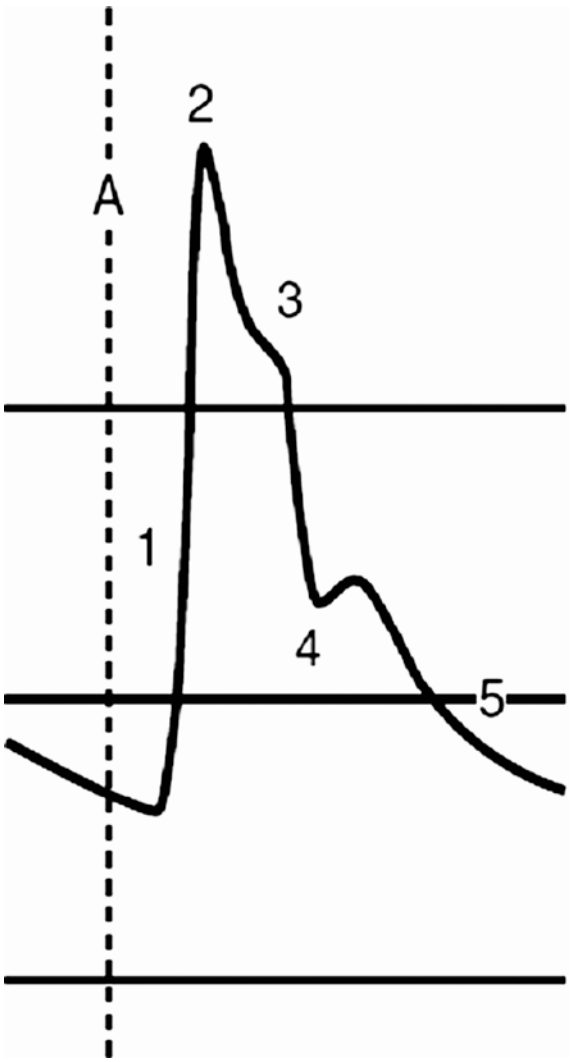
Troponin modulates calcium-mediated actin and myosin coupling in striated muscle. Cardiac troponin is made up of troponin I, C, and T subunits. Cardiac troponin I (cTnI) and cardiac troponin T (cTnT) have a unique N-terminal amino acid that allows differentiation from their skeletal muscle counterparts. cTnI is exclusively released from the myocardium, while cTnT can be released in small amounts from striated muscle. cTnT may be increased in renal failure, while cTnI is unaffected.

cTnI and cTnT were found to be highly sensitive and specific markers for myocardial damage in children and adults. Following myocardial injury, levels rise within 3–4 h, peak at 12 h, and are detectable for 10–14 days. Troponin levels have been utilized to support the diagnosis of myocarditis and/or pericarditis but do not reliably predict outcome. Troponin levels were found to correlate with the degree of myocardial injury in neonatal asphyxia and following congenital heart surgery. Of note, healthy newborns may demonstrate elevated troponin concentrations without clinical evidence of myocardial disease, which may be related to cesarean section delivery and/or intrauterine exposure to tocolytic therapy.

Review Questions

1. Which statement accurately reflects the utility of the physical assessment of the cardiovascular status of a child?
   A. Capillary refill time is independent of ambient temperature.
   B. Pulse pressure is decreased in conditions characterized by low systemic vascular resistance.
   C. Tachycardia, in and of itself, is a sensitive and specific sign of hemodynamic instability.
   D. The peripheral skin to ambient temperature gradient (dTp-a) decreases during states of high systemic vascular resistance.
   E. Urine output of 0.25–0.5 ml/kg/h is an appropriate therapeutic target during resuscitation of hypovolemic, septic, and distributive shock.

For questions 2–4, please refer to the arterial waveform figure below.

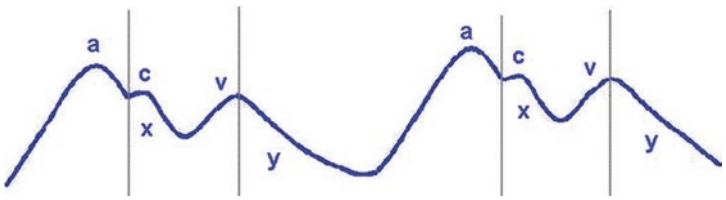


2. In the above illustration of an arterial waveform, which number identifies the incisura or dicrotic notch?
   A. 1
   B. 2
   C. 3
   D. 4
   E. 5

3. In the above illustration of an arterial waveform, which number identifies peak left ventricular ejection?
   A. 1
   B. 2
   C. 3
   D. 4
   E. 5

4. In the above illustration of an arterial waveform, which number identifies diastolic runoff?
   A. 1
   B. 2
   C. 3
   D. 4
   E. 5

For questions 5–8, please refer to the central venous pressure waveform figure below.



5. In assessing a normal central venous pressure (CVP) waveform, the c wave represents which of the following?
   A. The decline in atrial pressure that occurs during atrial relaxation and ventricular systole
   B. The displacement of the tricuspid valve toward the atrium during isovolumic ventricular contraction
   C. The fall in atrial pressure that occurs as the tricuspid valve opens and the atrium is drained
   D. The increase in intra-atrial pressure observed during atrial contraction that occurs at the end of ventricular diastole
   E. The rise in atrial pressure during the end of ventricular systole as the atrium fills with venous blood from the inferior and superior venous cava

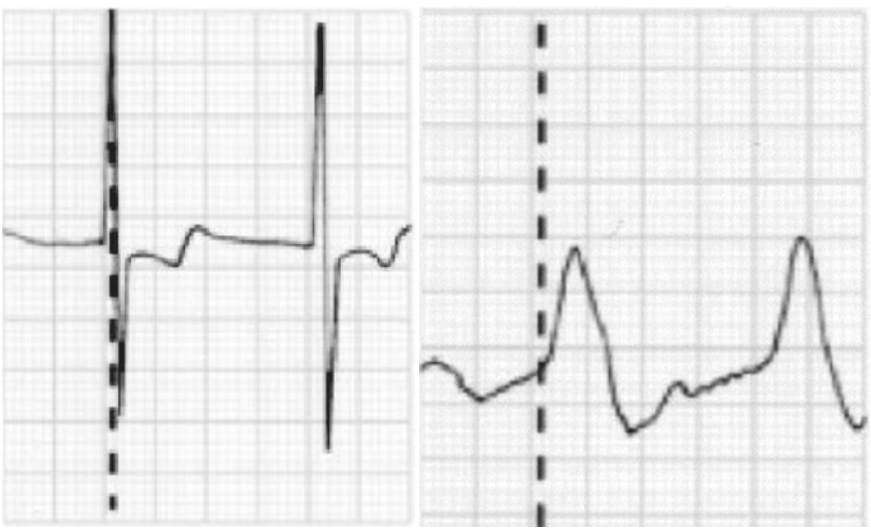
6. In assessing a normal central venous pressure (CVP) waveform, the x descent represents which of the following?
   A. The decline in atrial pressure that occurs during atrial relaxation and ventricular systole
   B. The displacement of the tricuspid valve toward the atrium during isovolumic ventricular contraction
   C. The fall in atrial pressure that occurs as the tricuspid valve opens and the atrium is drained
   D. The increase in intra-atrial pressure observed during atrial contraction that occurs at the end of ventricular diastole
   E. The rise in atrial pressure during the end of ventricular systole as the atrium fills with venous blood from the inferior and superior venous cava

7. In assessing a normal central venous pressure (CVP) waveform, the v wave represents which of the following?
   A. The decline in atrial pressure that occurs during atrial relaxation and ventricular systole

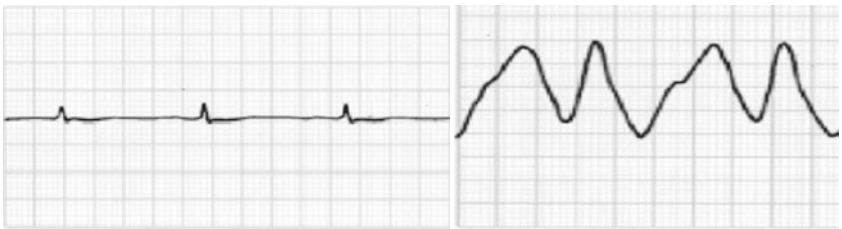
B. The displacement of the tricuspid valve toward the atrium during isovolumic ventricular contraction
C. The fall in atrial pressure that occurs as the tricuspid valve opens and the atrium is drained
D. The increase in intra-atrial pressure observed during atrial contraction that occurs at the end of ventricular diastole
E. The rise in atrial pressure during the end of ventricular systole as the atrium fills with venous blood from the inferior and superior venous cava

8. In assessing a normal central venous pressure (CVP) waveform, the y descent represents which of the following?
   A. The decline in atrial pressure that occurs during atrial relaxation and ventricular systole
   B. The displacement of the tricuspid valve toward the atrium during isovolumic ventricular contraction
   C. The fall in atrial pressure that occurs as the tricuspid valve opens and the atrium is drained
   D. The increase in intra-atrial pressure observed during atrial contraction that occurs at the end of ventricular diastole
   E. The rise in atrial pressure during the end of ventricular systole as the atrium fills with venous blood from the inferior and superior venous cava

9. Which statement is correct regarding arterial pressure monitoring systems?
   A. Damping describes the interaction between the oscillatory energy of a wave and the electrical properties of the monitoring system.
   B. Due to the turbulent flow and the high oxygen tension found in arteries, infections associated with arterial catheters are extremely uncommon.
   C. Pressure monitoring devices must be leveled to the point at which the catheter enters the artery.
   D. The delivery of a small "fast flush" to the arterial catheter allows for quantification of excessive resonance within the system.
   E. The phlebostatic axis is determined by locating the junction of the vertical line drawn down from the clavicle and the horizontal midaxillary line.



10. In assessing the above ECG and central venous pressure (CVP) waveform, which of the following is most likely?
    A. Severe tricuspid regurgitation
    B. Pulmonary hypertension
    C. AV dissociation
    D. Displacement of the tricuspid valve toward the atrium during isovolumic ventricular contraction
    E. Excessive rise in atrial pressure due to volume overload



11. In assessing the above ECG and central venous pressure (CVP) waveform, which of the following is most likely?
    A. Severe tricuspid regurgitation resulting in increased v wave
    B. RV noncompliance transmitting high diastolic pressure to atrium
    C. Tamponade physiology causing elevation of the CVP and equalization of diastolic filling pressures
    D. Tricuspid valve displacement toward the atrium during isovolumic ventricular contraction
    E. Atrial fibrillation

12. The right ventricular (RV) waveform and the pulmonary artery (PA) waveform can be distinguished from each other by which of the following?
    A. It is difficult to distinguish the waveforms without fluoroscopic visualization of the catheter tip.
    B. The PA diastolic pressure is usually greater than the RV diastolic pressure.
    C. The PA systolic pressure is usually greater than the RV systolic pressure.
    D. The RV diastolic pressure is usually greater than the PA diastolic pressure.
    E. The RV systolic pressure is usually greater than the PA systolic pressure.

13. Which disease state is most consistent with the following hemodynamic profile in a critically ill 10-year-old child?
    Heart rate: 129 bpm
    Blood pressure: 81/68 mm Hg
    Pulmonary artery occlusion pressure (PAOP): 24 mm Hg
    Pulmonary vascular resistance index (PVRI): 128 dyne-s/cm^5/m^2
    Cardiac index (CI): 2.0 L/min/m^2
    Central venous/right atrial pressure: 6 mm Hg
    Stroke volume index (SVI): 20 mL/beat/m^2
    Lactate: 10 mmol/L
    $SmvO_2$: 50%
    SaO_2: 91%
    A. Cardiomyopathy with biventricular dysfunction
    B. Congestive heart failure secondary to a large atrial septal defect with left to right shunting

C. Gastroenteritis with hypovolemia
D. Myocarditis with left ventricular dysfunction
E. Pulmonary hypertension with right ventricular dysfunction

14. Which of the following Fick derived equations is correct?

A. $CO = \frac{DO_2}{C_{Ao}O_2 - C_{pa}O_2}$

B. $Q_{pul} = \frac{C_{Ao}O_2}{C_{pv}O_2 - C_{pa}O_2}$

C. $Q_{pul}(C_{pv}O_2) = [Q_{pul}(C_{pa}O_2)] + DO_2$

D. $Q_{syst}(C_{pv}O_2) = [Q_{syst}(C_{Ao}O_2)] - VO_2$

E. $Q_{syst} = \frac{VO_2}{C_{Ao}O_2 - C_{pa}O_2}$

15. Which statement regarding the use of thermodilution to determine cardiac output is *MOST* correct?
A. A fundamental assumption during thermodilution is that the fluid injected into the right atrium will have complete and anatomically appropriate mixing prior to reaching the pulmonary artery.
B. A high cardiac output state results in a large area under the thermodilution curve.
C. Right heart cardiac output should equal left heart output even in the presence of an intracardiac shunt.
D. The area under the thermodilution curve is determined by the change in flow over time.
E. The area under the thermodilution curve is in the numerator of the Stewart-Hamilton formula used to calculate cardiac output.

16. A 6-year-old boy with chronic granulomatous disease presents with septic shock. Prior to arrival in the pediatric intensive care unit, he is intubated, is treated with antibiotics, receives fluid resuscitation with a total of 80 mL/kg of crystalloid, and is started on an infusion of dopamine at 15 mcg/kg/min. He has central arterial and venous access that allow for intermittent transpulmonary thermodilution and continuous pulse contour analysis for determination of the cardiac output.
The following hemodynamic data are obtained:
Heart rate: 138 bpm
Blood pressure: 88/34 mm Hg
Cardiac index (CI): 3.5 L/min/m^2
Central venous pressure: 6 mm Hg
Stroke volume variation (SVV) = 15% (normal <10%)
Systemic vascular resistance index (SVRI): 860 dyne-s/cm^5/m^2
Lactate: 12 mmol/L
$ScvO_2$: 45% (right atrium)
SaO_2: 91%
Hemoglobin: 8.5 mg/dL
Positive end-expiratory pressure (PEEP): 8 cm H_2O
Fraction of inspired oxygen (FiO_2): 0.65
The most appropriate next step in the management of this boy would be to:
A. Begin an infusion of epinephrine at 0.05 mcg/kg/min.
B. Begin an infusion of milrinone at 0.5 mcg/kg/min.
C. Begin an infusion of norepinephrine at 0.05 mcg/kg/min.
D. Continue volume resuscitation with an additional 20 ml/kg crystalloid.
E. Increase PEEP to 10 cm H_2O.

17. A 9-month-old infant with dilated cardiomyopathy presents in shock with severe left ventricular dysfunction. He requires intubation and the initiation of a milrinone infusion. He requires the addition of a nitroprusside infusion for afterload reduction. The nitroprusside infusion is titrated to 4 mcg/kg/min to maintain systolic blood pressure between 70 and 85 mm Hg. On the 6th PICU day, he develops a new metabolic acidosis with a base deficit (−7 mmol/L). A plasma lactate level is elevated (7.3 mmol/L) and the superior vena cava oxygen saturation is 88%. Which of the following explanations for an elevated lactate level is most worrisome in this clinical scenario?
    A. Decreased lactate clearance secondary to impaired renal clearance
    B. Elevated lactate production secondary to catecholamine-induced "hyperglycolysis"
    C. Impaired lactate metabolism secondary to an inborn error of metabolism
    D. Increased lactate production from tissue hypoperfusion
    E. Increased lactate production secondary to cellular inability to extract delivered oxygen

18. A 12-year-old girl with acute lymphoblastic leukemia is neutropenic and develops septic shock. Prior to arrival in the pediatric intensive care unit, she is treated with antibiotics and is fluid resuscitated with a total of 80 mL/kg of isotonic intravenous crystalloid fluids. She has both central arterial and venous catheters placed that allow intermittent transpulmonary thermodilution and continuous pulse contour analysis for cardiac output determination. She appears toxic and flushed and has a hyperbrisk capillary refill.
    The following hemodynamic data are obtained:
    Heart rate: 127 bpm
    Respiratory rate: 32 breaths per minute
    Blood pressure: 100/34 mm Hg
    Cardiac index (CI): 6.5 L/min/m^2.
    Central venous pressure: 16 mm Hg.
    Stroke volume index (SVI): 51 mL/beat/m^2
    Stroke volume variation (SVV) < 10% (normal <10%)
    Systemic vascular resistance index (SVRI): 400 dyne-s/cm^5/m^2
    Lactate: 9 mmol/L
    $ScvO_2$: 88% (right atrium)
    SaO_2: 100%
    Hemoglobin: 8.5 mg/dL
    The most appropriate next step would be to:
    A. Begin an infusion of epinephrine at 0.1 mcg/kg/min.
    B. Begin a transfusion of 15 ml/kg PRBCs.
    C. Begin an infusion of norepinephrine at 0.1 mcg/kg/min.
    D. Intubate and mechanically ventilate for impending respiratory failure.
    E. Diurese with furosemide (1 mg/kg).

19. A 12-year-old girl with acute lymphoblastic leukemia is neutropenic and develops septic shock. Prior to arrival in the pediatric intensive care unit, she is treated with antibiotics and is fluid resuscitated with a total of 80 mL/kg of isotonic intravenous crystalloid fluids. She has both central arterial and venous catheters placed that allow intermittent transpulmonary thermodilution and continuous pulse contour analysis for cardiac output determination. She appears toxic and flushed and has a hyperbrisk capillary refill.

The following hemodynamic data are obtained:
Heart rate: 127 bpm
Blood pressure: 100/34 mm Hg
Cardiac index (CI): 6.5 L/min/m^2
Central venous pressure: 16 mm Hg
Stroke volume index (SVI): 51 mL/beat/m^2
Stroke volume variation (SVV) < 10% (normal <10%)
Systemic vascular resistance index (SVRI): 400 dyne-s/cm^5/m^2
Lactate: 9 mmol/L
$ScvO_2$: 88% (right atrium)
SaO_2: 100%
Hemoglobin: 9.5 mg/dL
The elevated $S_{CV}O_2$ (88%) is likely indicative of which of the following?

A. Catheter tip positioning near the orifice of the coronary sinus
B. Drug toxicity
C. Inadequate oxygen uptake at the cellular level
D. Insufficient cardiac output to provide tissue perfusion
E. Successful resuscitation.

20. Which of the following is correct regarding central venous oxygen saturation ($ScvO_2$) and mixed venous oxygen saturation ($SmvO_2$)?

A. Decreased oxygen delivery raises both $ScvO_2$ and $SmvO_2$.
B. Decreased oxygen consumption lowers both $ScvO_2$ and $SmvO_2$.
C. In normal conditions, $SmvO_2$ is slightly higher than the $ScvO_2$.
D. $ScvO_2$ is best measured in the lower right atrium to reliably predict $SmvO_2$.
E. $SmvO_2$ is best measured in the right ventricle just below the tricuspid valve.

21. A 6-month-old male infant is 2 weeks postoperative from repair of tetralogy of Fallot. He underwent patch closure of the ventricular septal defect and relief of the right ventricular outflow obstruction with sparing of the pulmonary valve. He developed respiratory distress, poor oral intake, and progressive lethargy. He is admitted to the PICU with pneumonia, respiratory failure, and presumed septic shock. He is endotracheally intubated and administered saline fluid boluses (total = 20 mL/kg) and antibiotics. He remains cool and his pulses are weak. His capillary refill is 5 s. He has no JVD and his liver is palpated 1 cm below the right costal margin. His positive end-expiratory pressure (PEEP) is set at 7 cm H_2O and his peak inspiratory pressures range from 26 to 29 cm H_2O. An internal jugular central venous catheter with the tip positioned at the superior vena cava/right atrial junction and a radial arterial catheter are placed. His arterial catheter demonstrates a 25 mm Hg systolic pressure variation during a positive pressure breath. The following hemodynamic data are available:
Heart rate: 189 bpm
Blood pressure: 67/45 mm Hg
Central venous pressure: 14 mm Hg
Central venous oxygen saturation: 53%
Arterial oxygen saturation: 89% on 80% FiO_2
Arterial lactate: 6 mmol/L
Which one of the following statements is MOST correct?

A. The central venous pressure is consistent with adequate volume replacement.
B. The decreased arterial oxygen saturation is likely due to left to right shunting across a residual ventricular septal defect.

C. The hypotension is best corrected by the addition of an infusion of epinephrine.
D. The positive end-expiratory pressure needs to be reduced to increase right ventricular preload.
E. The hypotension is best corrected by additional intravenous volume replacement.

22. Which statement best describes wave frequency and resonance of pressure monitoring?
A. A system with high resonance may falsely increase the diastolic pressure by as much as 30%.
B. An accurate monitoring system at heart rates of ~180 beats per minute (bpm) should have its natural frequency equal 6 Hz.
C. If the frequency of the system is in the same range as the frequency of the arterial waveform, the amplitudes of the waves become additive and can overestimate the systolic pressure.
D. Resonant augmentation of the arterial pressure wave causes an artifactual increase in both systolic and diastolic recorded pressures.
E. The effect of resonance becomes less problematic when the monitoring system has a low natural frequency and the heart rate is high.

23. Which statement best describes the utility of focused cardiac ultrasound (FoCUS) in the PICU?
A. Ejection fraction utilizes the changes in LV volume, whereas fractional shortening utilizes changes in LV dimension to assess diastolic relaxation.
B. Assessments of systolic function, pericardial disease, valvular competence, and the presence of an intracardiac lesion can be rapidly assessed by FoCUS.
C. Normal values for FS in infants and children are between 20 and 30% assuming the ventricle has a symmetric cylindrical shape.
D. Measuring the maximal tricuspid valve regurgitation (TRV, m/sec) is used to estimate pulmonary artery systolic pressure utilizing the following equation: $\text{PASP} = 4 \times (\text{TRV max})^2$
E. The RV systolic pressure can be estimated by doubling the pulmonary artery systolic pressure: $\text{RVSP} = 2 \times \text{PASP}$

24. Which statement regarding near-infrared spectroscopy is correct?
A. NIRS technology is predicated on light absorption of three main chromophores: plasma proteins, oxygenated hemoglobin, and deoxygenated hemoglobin.
B. The majority of the NIRS measurement occurs in the venule compartment.
C. Light photons in the NIR spectrum are unable to penetrate dense structures such as the skull.
D. NIRS data provides absolute values for regional oxygen extraction.
E. Cerebral NIRS has been found to have greater utility in monitoring children status posttraumatic brain injury than in postoperative congenital heart repair.

25. Match the cardiac biomarker with the correct descriptions. Descriptions can be used more than once or not at all for each biomarker.
    Lactate
    NT-proBNP
    Troponin
    $ScvO_2$
    A. Following myocardial injury, levels rise within 3–4 h, peak at 12 h, and are detectable for 10–14 days.
    B. Using a cutoff of 100 pg/ml, the biomarker has a clinical specificity for heart failure of >96%.
    C. Levels can be elevated in newborns.
    D. Has been used as a marker of tissue hypoperfusion and anaerobic metabolism.
    E. Elevations may occur in the setting of impaired cellular and/or mitochondrial oxygen uptake.
    F. Is made up of three distinct subunits.
    G. Must be obtained from the central circulation.

Answers

1. D
2. D
3. B
4. E
5. B
6. A
7. E
8. C
9. D
10. C
11. C
12. B
13. D
14. E
15. A
16. C
17. E
18. C
19. C
20. C
21. E
22. C
23. D
24. B
25. See below
    Lactate - D. E.
    NT-proBNP - B. C.
    Troponin - A. C. F.
    $ScvO_2$ - D. E. G.

Suggested Reading

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Circulatory Failure/Shock

Stephen Pfeiffer and Hector R. Wong

Contents

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Learning Objectives

- Define shock.
- Describe the pathophysiologic changes that occur with the different classifications of shock.
- Understand the molecules that mediate the changes in the cardiovascular system during shock.
- Describe the role of cardiovascular monitoring in circulatory failure.
- State the mechanistic principles of goal-directed therapies (including use of lactate concentrations and venous oxygen saturations) aimed at improving outcome in children with circulatory failure.
- Define and understand the pathophysiology of multiple organ dysfunction syndrome.

17.1 Introduction

Shock is a common manifestation of many forms of critical illness. Although a patient with hypotension can have shock, shock is not necessarily defined by hypotension. That is, a patient can have a "normal" blood pressure and have shock concurrently. Accordingly, the definition of shock is based upon the balance between oxygen delivery, the circulation-related factors that govern oxygen delivery, and tissue oxygen requirements. When tissue oxygen requirements are not met by the circulatory system, be it due to poor myocardial function, hypovolemia, and/or hypotension, a patient is said to be in shock.

17.2 Shock Classifications

There are four broad forms and a miscellaneous category for shock, but other classifications may be used. The four forms are hypovolemic, distributive, cardiogenic, and septic. The latter may have elements of the other three categories. A fifth miscellaneous category includes obstructive forms of shock (e.g., tension pneumothorax, pulmonary embolus, and pericardial tamponade) as well as congenital cardiac lesions obstructing left or right ventricular output.

There are several classification schemes for shock, but a useful classification scheme is based on four broad forms of shock: cardiogenic shock, hypovolemic shock, distributive shock, and septic shock. Table 17.1 outlines the various subclassifications/etiologies that fall into these broad categories, as well as a miscellaneous classification. *Cardiogenic shock* implies primary myocardial failure such that there is an impaired ability of the heart to generate an adequate cardiac output to meet the tissue oxygen requirements. *Hypovolemic shock* implies that the intravascular volume has decreased to a level that reduces cardiac output, reduces tissue perfusion pressure, and/or reduces oxygen carrying capacity to levels that cannot meet the tissue oxygen requirements. *Distributive shock* can also be thought of as pathologic vasodilation. This implies a condition in which cardiac output and intravascular volume status may be adequate to meet tissue oxygen requirements, but blood flow is distributed in an aberrant manner (secondary to pathologic vasodilation) such that effective tissue perfusion is inadequate to meet the tissue oxygen requirements. In addition, increased venous capacitance secondary to venodilation can impair venous return to the heart. *Septic shock* merits a separate classification in that it can have concomitant manifestations of cardiogenic shock, hypovolemic shock, and distributive shock to varying degrees.

17.3 Determinants of Oxygen Delivery

In order to understand and treat shock, it is imperative to understand the determinants of oxygen delivery. Oxygen delivery is globally defined by the following equation:

$$\text{Oxygen Delivery} = \text{Cardiac Output} \times \text{Arterial Oxygen Content}$$

Table 17.1 Major classifications of shock and their subclassifications/etiologies

Major shock classification	Subclassification/etiology
Hypovolemic shock	Hemorrhagic shock
	Dehydration secondary to GI disorders
	Postoperative "third spacing"
	Fluid loss from surgical wounds or burns
Distributive shock	Anaphylactic shock
	Spinal shock secondary to spinal cord injury
	Unbalanced single ventricle physiology
Cardiogenic shock	Cardiomyopathy: dilated or restrictive myocarditis
	Postoperative low cardiac output syndrome
	Pulmonary hypertension
	Valve disease: regurgitant
	Bradycardia and tachyarrhythmia
Septic shock	Bacterial
	Viral
	Fungal
Miscellaneous	Left or right ventricular outflow obstruction
	Tension pneumothorax
	Pulmonary embolism
	Cardiac tamponade

The two major determinants of *cardiac output* are heart rate and stroke volume. Heart rate is a particularly important variable in the pediatric population due to age-dependent variations in heart rate (i.e., the newborn requires a higher heart rate for normal cardiac output than a 12-year-old child) and the remarkable capacity of the developing host to increase heart rate as a primary mechanism to compensate for shock. In addition, it is important to note that infants have a relatively fixed stroke volume, thus magnifying the impact of heart rate on cardiac output. The three major determinants of *stroke volume* are preload, afterload, and contractility. With these concepts in mind, it can be seen how hypovolemia (abnormal preload), pathologic vasodilation (abnormal afterload), and myocardial failure (abnormal contractility) can independently lead to decreased effective cardiac output and hence shock.

Arterial oxygen content (CaO_2) is determined by the hemoglobin concentration (Hgb), the arterial hemoglobin oxygen saturation (SaO_2), and the arterial partial pressure of oxygen (PaO_2):

$$CaO_2 = (1.34 \times Hgb \times SaO_2) + (0.003 \times PaO_2)$$

The factor of 1.34 refers to the oxygen carrying capacity of hemoglobin in mL O_2/g of hemoglobin, whereas the factor of 0.003 refers to the solubility coefficient of oxygen (mL oxygen/mm Hg) in plasma at 37 °C. From this equation, it can be seen that hemoglobin oxygen saturation and hemoglobin concentra-

Cardiac output is the product of heart rate and stroke volume; the latter is determined by preload, afterload, and cardiac contractility. The product of cardiac output and arterial oxygen content determines oxygen delivery.

Arterial oxygen content is determined mainly by the product of hemoglobin concentration and oxygen saturation with a minor contribution from the oxygen dissolved in plasma.

tion are the most important factors determining arterial oxygen content and the latter accounts, in large part, for the pathophysiology of hemorrhagic shock from the standpoint of oxygen delivery (see also ► Chap. 2).

17.4 Cardiogenic Shock

As stated previously, cardiogenic shock implies that there is primary failure of the myocardium such that the heart cannot generate a sufficient cardiac output to meet the tissue oxygen requirements. The most common form of cardiogenic shock results from systolic dysfunction as seen in myocarditis, cardiomyopathy, and low cardiac output syndrome following cardiopulmonary bypass and aortic cross-clamping during cardiac surgery. In this condition, there is decreased contractility leading to decreased stroke volume despite adequate preload and an appropriate afterload.

Cardiogenic shock is typically perceived to result from poor systolic pumping function, but cardiogenic shock less commonly results from abnormalities in diastolic function or from low or high heart rate. In the latter state, the diastolic filling time for coronary artery perfusion is compromised as myocardial oxygen demand increases. In addition, very rapid rates, especially if not coordinated with atrial contraction, may not provide adequate time and efficiency of ventricular filling leading to a low stroke volume.

Although systolic dysfunction is the more common cause of cardiogenic shock, abnormalities of heart rate or diastolic dysfunction, in the setting of normal systolic function, can also lead to cardiogenic shock. Thus, significant bradycardia can lead to low cardiac output and shock despite a normal stroke volume. Conversely, tachyarrhythmias can lead to cardiogenic shock secondary to compromise of diastolic filling time and/or eventual systolic dysfunction from excessive myocardial oxygen demand. Diastolic dysfunction occurs when there is decreased myocardial compliance such that ventricular filling during diastole is inadequate to generate a normal stroke volume during the subsequent systolic component of the cardiac cycle. A common clinical scenario in which right ventricular diastolic dysfunction is encountered is in the postoperative patient who has undergone tetralogy of Fallot repair. Many of these patients will have low cardiac output secondary to diastolic dysfunction during the immediate postoperative period until the hypertrophied right ventricle is able to "relax" and accommodate a normal systemic venous return (preload) in the setting of a closed ventricular septal defect. Other conditions that lead to low cardiac output and shock secondary to diastolic dysfunction include restrictive cardiomyopathies and cardiac tamponade.

17.5 Hypovolemic Shock

Any clinical condition that leads to a substantial net loss of intravascular fluid can lead to hypovolemic shock. For example, gastrointestinal diseases associated with vomiting and/or diarrhea are leading causes of death from hypovolemic shock in children worldwide, particularly in underdeveloped countries. Another example is the patient who has undergone an extensive surgical procedure and develops capillary leak syndrome during the postoperative period. These patients are prone to "third space" fluid in the extravascular compartment during the postoperative period. Although these patients can have a net positive fluid balance, they are at risk for developing hypovolemic shock, irrespective of postoperative bleeding, because the effective intravascular volume is inadequate to maintain a normal cardiac output. Thus, hypovolemic shock can be thought of as a preload abnormality. As intravascular fluid volume is decreased, the heart has less venous return during diastole (preload) and the resulting stroke volume is decreased, leading to shock. Shock secondary to hypovolemia typically implies a substantial net loss of intravascular volume given the compensatory mechanisms that can be activated in response to fluid loss. Children in particular are able to substantially increase their heart rate and thus maintain an adequate cardiac output despite a low intravascular volume/low stroke volume. Other compensatory mechanisms include reabsorp-

tion of fluid at the level of the kidneys by complex humoral mechanisms (e.g., vasopressin and the renin-angiotensin axis), shunting of blood to "more vital organs" (e.g., brain and heart) by complex vascular mechanisms involving the sympathetic and parasympathetic nervous systems, and mobilization of blood volume from the venous system.

Hemorrhagic shock is a more complex and somewhat unique form of hypovolemic shock for two broad reasons. First is the added and sometimes devastating component of decreased oxygen carrying capacity secondary to reductions in red blood cell mass. Thus, the patient with hemorrhagic shock is affected by both the aforementioned problems associated with a net decrease of intravascular volume (decreased cardiac output), as well as a reduced oxygen carrying capacity. The second factor is that patients with hemorrhagic shock will often develop multiple organ dysfunction syndrome (MODS) several days after their initial event. This syndrome can occur despite adequate surgical control of blood loss sources and seemingly adequate restoration of intravascular volume and red cell mass. It appears that massive blood loss activates a systemic reaction in the host, which causes tissue injury disproportionate to the initial insult of decreased intravascular volume and decreased red blood cell mass. This tissue and organ injury is also a manifestation of complex host mechanisms including activation of neutrophils, activation of endothelial cells, and oxidant injury related to the phenomenon of ischemia-reperfusion injury. In addition, massive requirement for transfusion of packed red blood cells, particularly red blood cells that have been in storage for several weeks, is associated with the development of transfusion-related acute lung injury.

Hypovolemic shock is the most common type in children. It is characterized by inadequate intravascular volume leading to impaired venous return and thus stroke volume, which compromises cardiac output. The typical compensatory mechanism to maintain cardiac output is tachycardia, remembering that cardiac output is the product of stroke volume and heart rate. Note that hypovolemia specifically refers to the intravascular volume; thus, children with capillary leak, such as after cardiopulmonary bypass or burn injury, may have increased total body water but inadequate *intravascular* volume.

Hemorrhagic shock is a more complex form of hypovolemic shock since tissue oxygen delivery is compromised both by low cardiac output and low arterial oxygen content if there is significant blood loss. Hemorrhagic shock can lead to multiple organ dysfunction that develops up to several days after the initial event due to complex mechanisms activated by ischemia-reperfusion.

17.6 Distributive Shock

Distributive shock typically results from profound abnormalities in vascular motor tone, otherwise known as pathologic vasodilation. On the arterial side of the circulation, pathologic vasodilation leads to profound hypotension, leading to decreased tissue perfusion pressure. Unlike other categories of shock where vasoconstriction leads to thready pulses with a narrow pulse pressure, patients with inappropriate vasodilation may maintain palpable distal pulses even with low blood pressure and the pulse pressure is characteristically wide. Although in pure distributive shock cardiac output is typically normal to supernormal, profound decreases in perfusion pressure can eventually lead to decreased coronary artery perfusion pressure and eventual myocardial dysfunction. Pathologic arterial dilation can lead to a maldistribution of blood flow such that arterial blood is shunted away from the vascular beds of vital organs to less vital regions such as the skin and muscle. There can also be maldistribution of blood flow within organs at the microcirculatory level and venodilation leading to increased capacitance of the vascular compartment leading to decreased preload. Anaphylaxis is the classic example of distributive shock seen in the clinical setting. In addition, anaphylaxis leads to loss of effective intravascular volume due to increased capillary permeability. Other conditions that can lead to distributive shock include spinal cord injuries, spinal or epidural anesthesia, and overdoses of medications with vasodilator properties.

Children with single ventricle physiology, particularly in the preoperative period and following a first stage Norwood operation, can also manifest a form of shock that can be considered a form of distributive shock. In this scenario, however, the manifestation of distributive shock is not secondary to pathologic vasodilation per se. Rather, it is due to the fact that the pulmonary and systemic vascular circulations have parallel connections (as opposed to the serial connection characteristic of normal physiology) supplied by a single ventricle

Distributive shock is characterized by pathologic vasodilation leading to maldistribution of blood flow at the macro- or microcirculatory level. Some organs may receive blood flow in excess of metabolic demand, while other organs, such as the splanchnic circulation, receive inadequate flow. Distributive shock is characterized by a wide pulse pressure with a low diastolic blood pressure. The vasodilation is not limited to the arterial circulation; relaxation of the capacitance venous system can lead to reduced venous return, exacerbating the hypotension that may occur in distributive shock. Anaphylaxis is the classic cause; spinal cord injury, epidural anesthesia, and overdoses of vasodilator medications are additional causes. Maldistribution of blood flow is also seen in patients with septic shock.

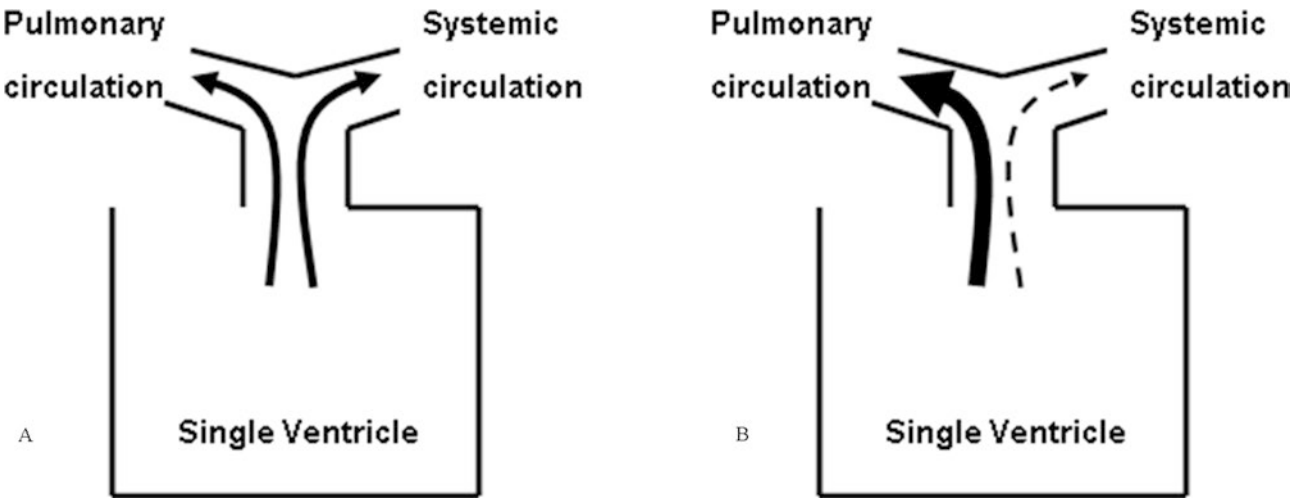

Fig. 17.1 Box diagram depicting single ventricle physiology in which one ventricle supplies pulmonary and systemic blood flow in a parallel circuit. In panel A, the resistances of the pulmonary and systemic circuits are well matched such that blood flow distribution is well balanced between the pulmonary and systemic vasculature. In panel B, the resistances of the pulmonary and systemic circuits are poorly balanced (decreased resistance in the pulmonary circuit and/or increased resistance in the systemic circuit) such that pulmonary blood flow is substantially increased at the expense of the systemic circulation. This situation can be considered as a form of distributive shock

Single ventricle physiology may cause a special form of distributive shock whereby systemic blood flow depends on maintaining a relatively high pulmonary vascular resistance to avoid pulmonary overcirculation and compromised systemic cardiac output.

(Fig. 17.1). In this condition, blood exits the single ventricle and can enter either the pulmonary circulation or the systemic circulation. The physical laws of fluid mechanics dictate that blood will preferentially flow along the path of least resistance. Thus, if the pulmonary vascular resistance is low and/or the source of pulmonary blood flow is not sufficiently restrictive, blood will preferentially flow into the pulmonary vasculature at the expense of the systemic vasculature. This results in a form of distributive shock because of decreased systemic blood flow (decreased systemic oxygen delivery), while the pulmonary vasculature is said to be "overcirculated" relative to the systemic vasculature.

17.7 Septic Shock

Septic shock is one of the most common conditions seen in pediatric critical care medicine. The clinical symptoms represent a manifestation of systemic infection as well as the host response to the infection. There are over 42,000 cases per year of pediatric septic shock in the United States, with a mortality rate of approximately 10%. Management of a patient with septic shock embodies the discipline of pediatric critical care medicine. The typical patient with septic shock has simultaneous derangements of cardiovascular function, intravascular volume status, respiratory function, immune/inflammatory regulation, renal function, coagulation, hepatic function, and/or metabolic function. The degree to which any of these derangements are manifest in a given patient is highly variable and influenced by multiple host and non-host factors including developmental stage, the presence or absence of comorbidities, the causative agent of septic shock, the primary site of infection, the host's immune/inflammatory state, and the host's genetic background. These factors combine, in turn, to profoundly influence the ultimate outcome of septic shock.

As stated previously, septic shock can be classified as a unique entity because it may have manifestations of all three aforementioned major classifications of shock: cardiogenic shock, distributive shock, and hypovolemic shock. Which of the three components predominates or is present in any given individual patient is highly variable, thereby presenting a significant therapeu-

tic challenge. The cardiogenic component of septic shock is manifested as a profound decrease in myocardial systolic function. Primary myocardial dysfunction is well documented in the setting of septic shock and is thought to be due to "myocardial depressant factors" in the serum of patients with septic shock. Compelling data suggest that tumor necrosis factor-α, interleukin-1β, and nitric oxide may all be responsible for this depressant activity. In addition, it has been suggested that primary myocardial dysfunction is a more common clinical scenario in the pediatric patient with fluid refractory septic shock compared with the adult patient with septic shock.

The distributive shock component of septic shock is similar to that previously described. That is, septic shock can be characterized by pathologic venodilation and vasodilation leading to profound hypotension and maldistribution of blood flow. The patient with septic shock that is primarily distributive is said to be in "warm shock," which is characterized by a vasodilated (warm/red skin, brisk pulses/capillary refill, and wide pulse pressure) and high cardiac output state. It has been suggested that this type of presentation of septic shock is much less common in the pediatric patient with fluid refractory septic shock compared to the adult patient with septic shock. Warm shock is more commonly observed in children with hospital-acquired septic shock, often associated with central venous catheters or other technology-associated devices, whereas cold shock is more commonly observed in community-acquired sepsis.

The hypovolemic shock component of septic shock is multifactorial. Many patients with septic shock have a net decrease of intravascular volume secondary to increased fluid losses (e.g., fever, vomiting, and diarrhea) and decreased fluid intake (e.g., transient anorexia). In addition, patients with septic shock can develop a profound capillary leak syndrome secondary to the generation of vasoactive mediators, which leads to "third spacing" of fluid into the extravascular space with a decreased effective intravascular volume. Finally, septic shock leads to pathologic venous and arterial dilation, as described above. Venodilation leads to decreased venous return. The consequence of this is increased intravascular capacitance such that the intravascular space is effectively increased relative to normal, thus creating a relative form of hypovolemia independent of fluid losses or the phenomenon of "third spacing."

Septic shock is a complex syndrome with variable pathophysiologic mechanisms leading to abnormalities in vascular tone, myocardial contractility, and intravascular fluid loss. The degree to which any of these derangements manifest in a given patient is highly variable and influenced by multiple host and non-host factors including the patient's developmental stage, the presence or absence of comorbidities, the causative agent of septic shock, the primary site of infection, the host's immune/inflammatory state, and the host's genetic background.

Since septic shock has different degrees of distributive, hypovolemic, and cardiogenic shock elements, careful patient assessment and individualized treatment should be based on your assessment of the patient's hemodynamic state, which may evolve over time.

17.8 Shock at the Cellular Level

The cellular manifestations of shock are protean. At the most fundamental level, however, shock is characterized by oxygen debt at the cellular level. This oxygen debt leads to interruption of oxidative phosphorylation, reliance on inefficient anaerobic metabolism, and subsequent depletion of ATP. If shock is sufficiently profound, ATP depletion leads to complete energy failure and necrotic cell death. If a significant number of cells undergo necrotic cell death, then whole organs begin to irreversibly fail leading to death of the patient secondary to MODS.

It is now well recognized that MODS occurs in patients despite seemingly adequate reversal of the shock state (i.e., normal cardiac output, normal intravascular volume status, normal blood pressure, and/or normal red blood cell mass). This realization has given rise to a large investigative discipline focused on the cellular responses that occur in the setting of shock. These investigations have provided substantial insight into the cellular and molecular mechanisms that lead to cell injury and death following shock. Some of these mechanisms will be discussed in the sections below.

Table 17.2 Characteristics of apoptosis and necrosis

Apoptosis	Necrosis
Single cells die	Groups of neighboring cells die
Cellular shrinkage and fragmentation	Cellular swelling
Plasma membranes intact	Cellular lysis
Mitochondria swell and release contents	Mitochondria swell; disordered structure
Organelles contract	Organelles swell; organelle disruption
Nuclear clumping and fragmentation	Nuclear membrane disruption
Internucleosomal DNA fragmentation	Diffuse and random DNA fragmentation
Phagocytosis of apoptotic cells with no inflammation	Inflammation; macrophage infiltration

At a cellular level, shock is characterized by inadequate oxygen delivery to the cell to meet its metabolic needs. Necrosis from cellular energy failure was thought to be the main outcome from this physiologic state, but shock may also stimulate programmed cell death (apoptosis), which is recognized as an additional important mechanism that may lead to MODS following shock resuscitation.

Failure of apoptosis by inflammatory cells may represent an important mechanism of ongoing tissue inflammation and consequent tissue damage that can occur following resuscitation from shock.

Apoptosis Apoptosis, or programmed cell death, refers to a form of cell death that is distinct from necrotic cell death. Although there are important overlaps and a continuum between these two forms of cell death, for purposes of discussion, the respective characteristics of apoptotic cell death and necrotic cell death are highlighted in Table 17.2. An important feature of apoptosis, from a therapeutic standpoint, is that it is an active and regulated process that requires energy and the coordinated expression and repression, respectively, of pro-apoptotic genes ("cell suicide" genes) and anti-apoptotic genes. In fetal biology, apoptosis is a normal occurrence that is crucial to normal organ and limb development. Apoptosis is also important in normal cell turnover (e.g., the gut epithelium) and in removal of potentially deleterious cell types (e.g., cancer). Thus, apoptosis can be viewed as being "beneficial" to the host. It has become increasingly recognized, however, that apoptosis also occurs in response to shock and in this setting apoptosis may be "detrimental" to the host. Evidence for widespread apoptosis abounds in animal models of shock as well as in humans with shock and is generally believed to be a maladaptive response that accounts, in part, for shock-associated MODS. One notable exception is apoptosis of neutrophils, which is thought to be an important mechanism for resolution of tissue inflammation. It has been suggested that failure of neutrophil apoptosis accounts, in part, for the prolonged tissue inflammation (and consequent tissue damage) that can occur during shock states. Nevertheless, shock-associated apoptosis has become an attractive therapeutic target because it is an active and regulated process and as such is potentially reversible through pharmacologic or genetic intervention.

Nitric oxide Nitric oxide (NO) is a gaseous molecule that is produced endogenously by a broad variety of cell types. It is produced during the conversion of arginine to citrulline by the enzyme nitric oxide synthase (NOS). There are three broad isoforms of NOS. The constitutive human isoforms, formerly referred to as neuronal NOS (nNOS) and endothelial NOS (eNOS), are now known as NOS 1 and NOS 3, respectively, based on the order in which they were cloned. Generally speaking, the constitutive isoforms are responsible for production of low levels of NO that are highly important in the regulation of various homeostatic processes

including vascular tone, signal transduction, and neurotransmission. NOS 2 is an inducible isoform (formerly known as inducible NOS, or iNOS) and is responsible for high and prolonged output of NO during various normal and pathologic biological conditions. High production of NO is thought to mediate pathologic vasodilation, myocardial suppression, and direct cellular toxicity.

Because NO has such a broad variety of biological functions, the exact role of NO in shock states remains controversial. This is particularly true in septic shock, where experimental evidence indicates that NO has both detrimental and beneficial effects in the setting of septic shock. For example, overproduction of NO has been clearly demonstrated in both adults and children with septic shock. In children, the amount of NO production has been correlated with non-survival and with vascular hyporesponsiveness to vasoconstrictors. Despite this evidence, as well as compelling preclinical data, therapeutic strategies targeting inhibition of NO production in human septic shock have not been of benefit.

Nitric oxide (NO) is an important secondary messenger that regulates numerous cellular systems such as signal transduction, neurotransmission, and microvascular tone. High production of NO facilitated by induction of NOS 2 is thought to mediate pathologic vasodilation, depression of myocardial contractility, and direct cellular toxicity, but inhibition of NO production in human septic shock trials was not beneficial.

PARP-1 Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear protein that senses and repairs DNA strand breaks that occur during various forms of cellular stress. In this capacity, PARP-1 is thought to play a beneficial role in shock states. In certain shock states, however, PARP-1 is thought to be overactivated and leads to cellular injury. This occurs because high level PARP-1 activity consumes NAD(+) and can consequently deplete ATP, thereby leading to cellular death secondary to energy failure. In addition, PARP-1 activation plays a role in the apoptosis pathway. Accordingly, there is a great deal of ongoing research focused on inhibition of PARP-1 activity in shock states.

NF-κB As previously mentioned, many shock states are characterized by a highly activated inflammatory response. Many of these inflammatory responses are centrally regulated by nuclear factor-κB (NF-κB). NF-κB is a transcription factor that regulates the expression of many genes involved in the innate immune response and inflammation pathways. These include cytokines, chemokines, and NOS 2. In addition, NF-κB has both pro- and anti-apoptotic activity. Because NF-κB is a central regulator of inflammation, there has been considerable interest in elucidating the role of NF-κB in shock states. Studies have clearly demonstrated increased activation of NF-κB in shock states; inhibition of NF-κB activation has been demonstrated to be beneficial in various animal models of shock. In humans with septic shock, the degree and duration of NF-κB activation has been correlated with mortality. In this regard, it is interesting to note that corticosteroids are potent inhibitors of NF-κB activation.

HIF-1 Hypoxia-inducible factor-1 (HIF-1) is also a transcription factor, which functions as a cellular-level "sensor" of hypoxia, a common manifestation of all shock states. Active HIF-1 is composed of two subunits: HIF-1α and HIF-1β. Both subunits are constitutively present in the cytoplasm, but under conditions of normoxia, the HIF-1α subunit is degraded by the ubiquitin-proteasome pathway. Under conditions of cellular hypoxia, however, the degradation of HIF-1α is terminated, thus allowing for the formation of HIF-1α/HIF-1β heterodimers, which are active and can translocate to the nucleus to increase the expression of various genes required for adaptation to hypoxia. These include erythropoietin, vascular endothelial growth factor, heme oxygenase, NOS 2, and various genes related to glucose metabolism. Thus, HIF-1 activation is potentially an important compensatory/adaptive mechanism during shock, and its regulation during shock states is a fruitful area of investigation.

Ischemia-reperfusion/oxidant injury All forms of shock have the potential to lead to ischemia-reperfusion injury. As the term for this form of injury implies, cellular injury is a manifestation of both the duration of low blood flow/low oxygen delivery (ischemia) and the restoration of normal blood flow/normal oxygen delivery (reperfusion). Thus, while the latter is an obvious therapeutic goal in the clinical setting, paradoxically, when blood flow and oxygen delivery are restored to normal (sometimes supernormal) levels, this process can itself exacerbate cellular and tissue injury, which has led to the recommendation to avoid arterial oxygen saturations greater than 96% in acutely ill patients. The process of reperfusion injury is highly complex but seems to be mediated in large part by the generation of free radical oxygen species during restoration of normal blood flow and oxygenation. The oxygen free radicals are intrinsically injurious to cells and tissues by damaging intracellular proteins and cellular membranes. In addition, these oxygen-derived free radicals can act as signaling molecules that can lead to various potentially cytotoxic events such as neutrophil and endothelial activation, cytokine production, activation of apoptosis, complement activation, expression of NOS 2, and PARP-1 activation. Accordingly, another important investigative effort is focused on ameliorating the potentially deleterious effects of reperfusion injury by free radical scavenging strategies.

Toll-like receptors Toll-like receptors (TLRs) are central to the cellular response to pathogens. TLRs are molecules that recognize pathogen-associated molecular patterns (PAMPs). Well-described PAMPs include lipopolysaccharide (gram-negative bacteria), peptidoglycan and lipoteichoic acid (gram-positive bacteria), double-stranded RNA (viruses), bacterial DNA, and flagellin (bacteria that possess flagella). TLRs are membrane-associated receptors that allow cells of the innate immune system to detect the presence of pathogens associated with septic shock. While pathogen recognition is vital for host defense mechanisms, TLR activation can also lead to the initiation of the various inflammatory cascades that contribute to the pathophysiology of septic shock. This has led to some investigation of TLRs (specifically TLR4) as therapeutic targets in sepsis. Some of the more well-studied TLRs and the specific PAMPS that are recognized by them are listed in ◘ Table 17.3.

Heat shock proteins Heat shock proteins (HSPs) are a broad group of intracellular proteins that serve as molecular chaperones. In this capacity, HSPs serve to stabilize, transport, and refold damaged intracellular proteins. HSP expression was first described in response to hyperthermia, hence the term "heat shock pro-

Multiple mediators operating at the cellular level affect the outcome of patients with shock. These include the following:

- *Poly(ADP-ribose) polymerase-1* (*PARP-1*) is a nuclear protein that senses and repairs DNA strands and is thought to cause injury during cellular hypoxia because it consumes NAD(+) which depletes ATP, thereby leading to cellular death secondary to energy failure.
- Many shock states are characterized by an activated inflammatory response, which is at least partly centrally regulated by *nuclear factor-κB* (NF-κB). NF-κB is a transcription factor that regulates the expression of many genes involved in the innate immune response and inflammation pathways.
- *Hypoxia-inducible factor-1* (*HIF-1*) is also a transcription factor, which functions as a cellular-level "sensor" of hypoxia, a common manifestation of all shock states. HIF-1 activation is potentially an important compensatory/

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◘ **Table 17.3** Selected Toll-like receptors (TLRs) and their respective pathogen ligands

Receptor	Ligand
TLR1	Lipopeptides (bacteria)
TLR2	Peptidoglycan and lipoteichoic acid (gram-positive bacteria), HSP70
TLR3	Double-stranded RNA (viruses)
TLR4	Lipopolysaccharide (gram-negative bacteria), several HSPs
TLR5	Flagellin (flagella-bearing bacteria)
TLR6	Lipopeptides (mycoplasma)
TLR9	Bacterial DNA

teins." It is now known, however, that HSPs are also highly expressed in various forms of cellular stress, including shock. In this capacity, HSPs confer cellular protection against various forms of cellular injury including ischemia-reperfusion, hypoxia, and oxidant stress. Much of these cytoprotective effects appear to be mediated by the inducible isoform of HSP70. Apart from their molecular chaperone properties, activation of heat shock proteins also appears to have an inhibitory effect on activation of the NF-κB pathway described above. Extracellular levels of both HSP70 and HSP60 were found to be elevated in children with septic shock.

17.9 Clinical Monitoring of Shock

Clinical Despite technological advances in critical care medicine, physical exams and basic clinical parameters continue to be important "monitors" of shock. The following are key physical signs and basic clinical parameters that can assist in both detecting shock states and gauging the patient's response to therapy. *Low blood pressure* is highly suggestive of shock, but always remember that shock can be present in the setting of a normal blood pressure. Thus, restoration of a normal blood pressure should not be the only endpoint for shock-related therapy. Indeed, the optimal blood pressure is not known and achieving a specified blood pressure by excessive vasoactive drug-induced vasoconstriction may actually impair the goal of shock therapy: restoring adequate tissue perfusion. *Tachycardia* is a fundamental compensation for shock and resolution of tachycardia, particularly in hypovolemic shock, is a good indicator that the appropriate therapeutic endpoint (i.e., volume restoration) has been reached. *Decreases in pulse amplitude and/or perfusion* are also good clinical indicators of shock and are often evident before the onset of hypotension. *The pulse pressure* can also be highly informative. For example, a narrow pulse pressure is expected in the setting of hypovolemic or cardiogenic shock. Alternatively, a wide pulse pressure (manifested as bounding pulses and very brisk perfusion) can be seen in distributive shock and hyperdynamic septic shock. *Heart auscultation* can reveal an S_3 or S_4 sound ("gallop" rhythm) indicative of myocardial dysfunction. *Alterations in mental status* can also be a manifestation of shock, but it should be remembered that this is a relatively late sign of shock due to the various compensatory mechanisms that maintain cerebral blood flow. In sepsis, however, alterations in mental status may occur as an early manifestation. More often, other clinical signs of shock are likely to be present in other types of shock before alterations in mental status are clinically evident. *Increased work of breathing* with grunting may be seen in children with cardiogenic shock due to pulmonary edema, but may also be seen in children with pneumonia and sepsis. Finally, adequate *urine output* remains a valuable indicator of shock or shock resolution. Interpretation of urine output, however, must be made in the context of various confounding factors such as concomitant use of diuretics and/or intrinsic renal disease.

Acid-base status Since shock is defined by an insufficient delivery of oxygen to meet tissue oxygen demands, it is expected that shock leads to abnormalities in acid-base status. Specifically, shock can lead to increased dependence on anaerobic metabolism, which results in overproduction of lactate and protons. The classic scenario in shock states is the presence of an increased anion gap metabolic acidosis secondary to increased lactate production. Thus, serial measurement of arterial blood gases to identify the presence of a metabolic acidosis, and lactate concentration can serve as a guide for the severity, evolution, and resolution of shock. It should be stressed that serial measurements are of more practical value than isolated measurements.

adaptive mechanism during shock, and its regulation during shock states is a fruitful area of investigation.

- All forms of shock may cause *ischemia-reperfusion injury*. Reperfusion injury is a highly complex process that seems to be mediated in large part by the generation of free radical oxygen species during restoration of normal blood flow and oxygenation. The oxygen free radicals injure cells and tissues by damaging intracellular proteins and cellular membranes. In addition, they can act as signaling molecules leading to various potentially cytotoxic events such as neutrophil and endothelial activation, cytokine production, activation of apoptosis, complement activation, expression of NOS 2, and PARP-1 activation. To reduce reperfusion injury, many post-shock/resuscitation guidelines recommend maintaining arterial oxygen saturation <97%.
- *Toll-like receptors* (*TLRs*) are central to the cellular response to pathogens. TLRs are molecules that recognize pathogen-associated molecular patterns (PAMPs). While pathogen recognition is vital for host defense mechanisms, TLR activation can also initiate various inflammatory cascades that contribute to the pathophysiology of septic shock.
- *Heat shock proteins* (*HSPs*) are a broad group of intracellular proteins that serve to stabilize, transport, and refold damaged intracellular proteins. In addition to hyperthermia, HSPs are also highly expressed in various forms of cellular stress, including shock. In this capacity, HSPs confer cellular protection against various forms of cellular injury including ischemia-reperfusion, hypoxia, and oxidant stress.

Clinical signs provide insight into the type of shock. Low blood pressure is not required to diagnose shock. Tachycardia is a common compensatory response to a fall in stroke volume. A narrow pulse pressure (weak pulse) with decreased clinical perfusion is consistent with hypovolemic or cardiogenic shock, whereas a wide pulse pressure is characteristic of distributive shock and is common in septic shock. The presence of a gallop rhythm is consistent with cardiogenic shock. Alterations in mental status are often a late sign of shock but may be an early sign in sepsis.

An increased work of breathing with grunting suggests pulmonary edema due to cardiogenic shock or pneumonia and septic shock.

Increased lactate concentrations are often considered a marker of anaerobic metabolism and shock but should be interpreted in the context of the patient's acid-base balance since lactate may be increased for reasons unrelated to tissue hypoxia, such as increased gluconeogenesis mediated by endogenous or exogenous corticosteroids.

It should also be stressed that multiple factors, other than insufficient oxygen delivery, can affect acid-base status and lactate concentration. For example, liver dysfunction is associated with decreased metabolism of lactate, which in turn can lead to increased blood lactate concentrations that do not necessarily reflect increased lactate production. Furthermore, the laboratory measures lactate and not lactic acid; lactate may be increased without a metabolic acidosis, such as due to increased gluconeogenesis stimulated by endogenous or exogenous corticosteroids. Another notable example is loss of bicarbonate in the setting of severe diarrhea (hypovolemic shock). In this setting, patients can have a mixed source of metabolic acidosis: normal anion gap metabolic acidosis secondary to bicarbonate loss plus an anion gap acidosis (lactic acidosis) secondary to hypovolemic shock. Infusion of large amounts of fluid with high chloride content (e.g., normal saline) can also lead to a non-anion gap hyperchloremic metabolic acidosis, and there are recent reports of an independent association between hyperchloremia and poor outcomes among children with septic shock. Comorbid conditions also need to be considered when assessing acid-base status in the setting of shock. For example, a patient who has been on chronic, high-dose diuretic therapy or a patient that has chronic respiratory failure (hypercarbia) is likely to have a high baseline bicarbonate concentration. When these patients develop metabolic acidosis secondary to shock, the serum bicarbonate concentration may be in a normal range, but it should be recognized that their bicarbonate concentration has decreased significantly from the higher pre-shock level. Thus, it is imperative that serial measurements of arterial blood gases and lactate, in the setting of shock, be interpreted within the context of the multiple factors that can affect acid-base status independently of shock.

Pulmonary artery catheter The pulmonary artery catheter (PAC) remains the gold standard for objectively assessing oxygen delivery in the critically ill patient. ▶ Box 17.1 provides a condensed list of the variables that can be directly measured by a PAC and the variables that can be derived from these measurements. In this context, the PAC would seem to be an indispensable tool for the management of shock. Indeed, for many years, PACs were placed routinely in adults for a broad range of clinical conditions. Insertion of a PAC, however, carries important risks to the patient that are likely to be exacerbated in the smaller pediatric patient. Importantly, the utility and appropriateness of routine PAC insertion have come under very strong criticism, with some leaders in the field going as far as proposing a ban on the use of PACs. As this debate continues with considerable intensity, it is difficult to advocate for the routine use of PACs in pediatric patients with shock. It seems reasonable, however, to consider insertion of a PAC in pediatric patients with severe and complex forms of shock. As always, this must be considered in the context of the potential iatrogenic complications that can occur with PAC placement and the available clinical experience necessary to accurately interpret PAC-derived data.

Box 17.1 Selected variables measured by pulmonary artery catheters

Direct measurements

- Cardiac output
- Central venous pressure
- Pulmonary artery pressure
- Pulmonary capillary wedge pressure
- Mixed venous oxygen saturation

Derived measurements
- Oxygen delivery
- Oxygen consumption
- Oxygen extraction ratio
- Systemic vascular resistance
- Pulmonary vascular resistance

Mixed venous oxygen saturation Mixed venous oxygen saturation ($S_{mv}O_2$) is measured in the pulmonary artery after complete mixing of the venous return; this parameter can serve as a valuable objective measurement of oxygen delivery and consumption in shock states. The relationship between oxygen delivery and $S_{mv}O_2$ can be understood by the Fick principle:

$$\text{Oxygen Consumption} = \text{Cardiac Output} \times \left(\text{Arterial } O_2 \text{ content} - \text{Venous } O_2 \text{ content}\right)$$

This equation can be solved for cardiac output as follows:

$$\text{Cardiac Output} = \text{Oxygen Consumption} \div \left(\text{Arterial } O_2 \text{ content} - \text{Venous } O_2 \text{ content}\right)$$

The equation can be further modified by changing arterial O_2 content to arterial saturation (S_aO_2) and venous O_2 content to $S_{mv}O_2$:

$$\text{Cardiac Output} \cong \text{Oxygen Consumption} \div \left(S_aO_2 - S_{mv}O_2\right)$$

From this last equation, it can be seen that decreased $S_{mv}O_2$ yields a larger number in the denominator of the equation. If oxygen consumption and arterial oxygen content are constant, then a lower $S_{mv}O_2$ reflects a lower cardiac output. Physiologically, the fall in $S_{mv}O_2$ results from increased tissue uptake of oxygen when tissue blood flow and/or arterial oxygen content is reduced. Thus, decreases of $S_{mv}O_2$ suggest a decrease of oxygen delivery secondary to decreased cardiac output. The variables in this equation, however, are not always constant in the critically ill patient. For example, hypoxemia and/or anemia decreases arterial oxygen content. If the cardiac output and oxygen consumption are relatively constant in this context, then the $S_{mv}O_2$ would have to be lower based on this equation. In a similar manner, if oxygen consumption is increased, and cardiac output and arterial oxygen content are constant, then the $S_{mv}O_2$ also would have to decrease based on this equation.

In the absence of a pulmonary artery catheter, the oxyhemoglobin saturation of central venous blood sampled from the high right atrium ($S_{cv}O_2$) has become a widely accepted estimate of the mixed venous oxyhemoglobin saturation ($S_{mv}O_2$). Serial measurements of $S_{cv}O_2$ can serve as objective, indirect measurements of global oxygen delivery. Decreased $S_{cv}O_2$ can be indicative of inadequate oxygen delivery, while increases of $S_{cv}O_2$ in response to therapy can be indicative of effective therapy for shock. As stated above, however, changes in $S_{cv}O_2$ can also be indicative of changes in oxygen consumption or changes in arterial oxygen content. The latter can be readily estimated at the bedside (i.e., hemoglobin and pulse oximetry), thus leaving oxygen consumption as the only other "unknown" variable. This is important because it cannot be assumed that oxygen consumption is constant in the critically ill patient. For example, oxygen consumption increases by 10–13% for each 1 °C increase in temperature; thus, significant fever can lead to decreased $S_{cv}O_2$. Alternatively, some

Ideally, mixed venous oxygen saturation ($S_{mv}O_2$) is measured in the pulmonary artery after complete mixing of the venous return, but since pulmonary artery catheters are uncommonly used, central venous oxygen saturation ($S_{cv}O_2$) measured just above the right atrium is often used instead. This parameter can provide a valuable objective assessment of the balance between oxygen delivery and consumption in shock states. Serial measurements of $S_{cv}O_2$ are especially useful as an indirect measurements of changes in global oxygen delivery and consumption in response to therapy.

Factors that can decrease $S_{cv}O_2$ are decreased cardiac output, decreased arterial oxygen content (low hemoglobin and/or low arterial oxygen saturation), and increased tissue metabolic demand.

patients with shock (particularly septic shock) are unable to adequately consume oxygen. This would be reflected as a high or normal S_vO_2 that could be inappropriately interpreted as a sign of adequate oxygen delivery.

Even when a central venous catheter is not available, relatively recent technology based on near-infrared and visible light spectroscopy provides noninvasive and clinically feasible estimates of $S_{cv}O_2$. These probes may be placed on the forehead and over the liver, kidney, or other organ to continuously estimate venous oxygen saturation in that body region.

Variables that can affect $S_{mv}O_2$ include intracardiac shunts (left to right) and catheter tip placement. As stated above, the ideal catheter tip placement for measuring $S_{mv}O_2$ is the pulmonary artery since this site represents the most complete mixing of venous blood return. It has been demonstrated, however, that placement of a catheter tip at the junction of the superior vena cava and the right atrium ($S_{cv}O_2$) provides a clinically reasonable estimate of $S_{mv}O_2$.

The value of superior vena cava-derived $S_{cv}O_2$ data was demonstrated in a randomized trial involving adult patients with septic shock. Patients were randomized to one of two treatment protocols, and importantly, protocol-based therapy was instituted during the first 6 hours of presentation to the emergency department, prior to transfer to the intensive care unit. In one protocol cohort, patients received therapy targeting "traditional" endpoints such as central venous pressure, blood pressure, and urine output (standard therapy group). The other protocol cohort targeted similar endpoints but added $S_{cv}O_2$ measurements ($\geq$70%) as the goal endpoint for therapy (goal-directed therapy group). $S_{cv}O_2$ measurements were taken from central venous catheters placed in the superior vena cava.

While this initial study showed improved survival, more recent trials (ProCESS, ARISE, ProMISe) have not shown an attributable survival benefit for $S_{cv}O_2$ measurement-directed therapy, relative to standard care. In addition, $S_{cv}O_2$ measurement-directed therapy increases the cost of care. While not studied extensively in the pediatric patient in shock, there are some data suggesting that resuscitation directed at normalization of $S_{cv}O_2$ (i.e., an oxygen saturation $\geq$70%) can improve outcomes in the setting of pediatric septic shock, but the sample size was small and the baseline mortality rate of the standard care group was relatively high, thus calling into question the generalizability of these data.

17.10 Therapy for Shock

For all forms of shock, there are two equally important levels of therapy: etiology-specific therapy and supportive therapy. In all cases of shock, the direct cause of shock should be addressed if possible. For example, in hemorrhagic shock, there often needs to be surgical intervention to curtail ongoing blood loss. In septic shock, antibiotics and source removal continue to be mainstays of therapy. In anaphylactic shock, it is crucial to discontinue and avoid further contact with the antigenic stimulus, when known. In cardiogenic shock, anatomic causes of myocardial failure (e.g., coarctation of the aorta) need to be addressed surgically.

Often, however, there are no specific therapeutic strategies to address the underlying cause of shock. In this scenario, supportive therapy becomes the mainstay of therapy. These supportive therapies will be the focus of the subsequent sections and will not include mechanical approaches such as extracorporeal membrane oxygenation, ventricular assist devices, and intra-aortic balloon pumps. The need to address the specific cause of shock, when feasible, cannot

be overstated but will not be repeated in each of the following sections. The therapeutic endpoints discussed in the previous section are potentially applicable for all of the following supportive therapies.

Hypovolemic shock The primary supportive therapy for hypovolemic shock is restoration of intravascular volume. The type of intravenous fluid that is used for volume restoration will vary depending on the cause of hypovolemia. In hypovolemic shock secondary to vomiting and diarrhea, crystalloid replacement is usually sufficient. The type of crystalloid depends on the presence or absence of associated electrolyte disturbances (e.g., hypo- or hypernatremia). The use of albumin as the replacement fluid for hypovolemic shock is probably best reserved for situations associated with direct loss of albumin (e.g., burns, open wounds, protein-losing enteropathies). In cases of hemorrhagic shock, volume replacement with crystalloid or albumin can be appropriate, but with significant blood loss, replacement of red blood cell mass will eventually become a necessity. In the setting of large volume red blood cell transfusion requirements, consideration also needs to be given to replacement of other blood components such as platelets and plasma. Ongoing work in the adult trauma literature, including studies related to battlefield casualties, indicates that the ratio of red blood cells to other blood components (i.e., plasma and platelets) is a critical outcome factor for patients with massive hemorrhage and that the ratio may be lower than advocated by traditional practice (e.g., plasma-to-RBC ratio between 1:1 and 1:2).

While most patients with hypovolemic shock tolerate relatively rapid correction of intravascular volume depletion, there are some notable exceptions that may require less rapid correction. For example, in cases of hypovolemic shock that are accompanied by significant metabolic/electrolyte derangements (e.g., hypernatremia or diabetic ketoacidosis), volume deficit correction must be tempered so as to not correct the accompanying metabolic/electrolyte abnormalities too rapidly. In patients with underlying myocardial dysfunction, correction of hypovolemic shock must be done more judiciously than that of a patient with normal myocardial function so as to not further compromise myocardial function. Finally, there may be trauma-specific situations in which very aggressive volume resuscitation for hemorrhagic shock is not appropriate until surgical control of hemorrhage is achieved.

Shock treatment consists of etiology-specific therapy and general supportive measures. In hypovolemic shock, the main supportive therapy is restoration of intravascular volume, typically provided with isotonic crystalloid. In most children, this can be infused rapidly, but fluid should be given more slowly in children with diabetic ketoacidosis or concomitant impaired cardiac function. If there is blood loss, such as with trauma, red blood cells may be required. If there is a need for substantial blood transfusion, fresh frozen plasma and platelets should also be given.

Cardiogenic shock Assuming that the heart rate is appropriate, the therapeutic strategies for cardiogenic shock are focused on optimizing stroke volume. This entails optimization of the three aforementioned components of stroke volume: preload, afterload, and contractility. In addition, consideration can be given to decreasing metabolic demand, when feasible. For example, fever can be reduced pharmacologically or mechanically, and increased respiratory effort can be mitigated with mechanical ventilation as a means to reduce metabolic demand.

Optimization of preload can consist of either administration of volume to increase preload or administration of diuretics to decrease preload. The physiologic principle for basing this decision is depicted in ◘ Fig. 17.2, a theoretical Starling curve. Admittedly, it is sometimes difficult to correctly assess clinically where on the Starling curve a particular patient is functioning. Helpful adjuncts include central venous pressure (CVP), responses to fluid challenge, and chest radiographs. The optimal CVP will vary from patient to patient because CVP is influenced by factors other than intravascular volume including myocardial compliance, intrathoracic pressure, and catheter tip placement. All of these factors must be taken into consideration when interpreting and optimizing CVP. There is, in fact, a degree of "trial and error" that must sometimes occur in order to optimize CVP at the bedside. For example, a fluid challenge that

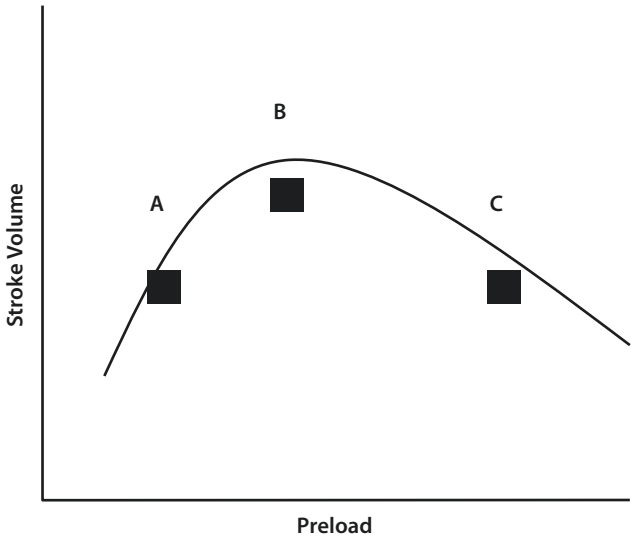

Fig. 17.2 Theoretical Starling curve in which stroke volume (y-axis) is dependent on preload (x-axis) with the assumption that myocardial contractility and afterload are constant. Point B is the ideal preload at which stroke volume is maximal for a given state of contractility and afterload. Point A depicts a condition in which additional preload (i.e., intravascular volume) is necessary to optimize stroke volume. Point C depicts a condition in which less preload (i.e., diuretic administration) is necessary to optimize stroke volume. Note that preload is not the same as CVP; changes in ventricular compliance complicate the estimation of preload from filling pressure

does not change CVP, but leads to a decrease of heart rate and an improvement in perfusion and urine output, likely means that the patient needs further, judicious administration of fluid to optimize preload. Conversely, a fluid challenge that leads to a large increase in CVP with increased heart size and pulmonary edema on chest radiograph, but no concomitant improvement in urine output or perfusion, likely means that the patient needs diuretics to optimize preload.

Additional bedside metrics to help assess fluid balance include the use of the passive leg raise (PLR) test. The PLR consists of using continuous cardiopulmonary monitoring while laying the patient flat and elevating one or both legs to 45°, which effectively displaces fluid from the leg(s) into the intrathoracic cavity. This ultimately gives the patient a fluid bolus of approximately 5% of their blood volume that if deleterious can be quickly removed by lowering the leg. A patient is deemed fluid responsive if stroke volume increases by approximately 10%, which if present carries a high degree of sensitivity and specificity for fluid responsiveness.

The use of ultrasound to assess IVC caliber as a measure of fluid responsiveness has also been investigated. To date, the degree of clinician variability in assessing IVC caliber and thereby fluid responsiveness makes the use of ultrasound less reliable in predicting fluid responsiveness.

Afterload reduction (reduction of systemic and/or pulmonary vascular resistance) can be a very effective approach to optimizing stroke volume. The rationale for afterload reduction is based on the equation describing systemic vascular resistance (SVR):

$$\text{SVR} = \left(\text{Mean Arterial Pressure} - \text{Central Venous Pressure}\right) \div \text{Cardiac Output}$$

Solving this equation for cardiac output yields the following equation:

$$\text{Cardiac Output} = \left(\text{Mean Arterial Pressure} - \text{Central Venous Pressure}\right) \div \text{SVR}$$

From this equation, it can be seen that if mean arterial pressure and central venous pressure remain relatively constant, then a reduction in SVR is accompanied by an increase in cardiac output (stroke volume). Measuring SVR requires direct measurement of cardiac output (e.g., pulmonary artery catheter). It is clinically feasible and appropriate, however, to manipulate SVR without the use of invasive monitoring. In this more common scenario, medications for afterload reduction are titrated to clinical improvements in cardiac output (described previously) with the limiting factor being hypotension. Common medications for afterload reduction include sodium nitroprusside, milrinone, angiotensin-converting enzyme inhibitors, and nicardipine. An important caveat to optimal afterload reduction is that the patient first needs to have an optimal preload. Furthermore, since many of these agents increase venous compliance, fluid may be needed to maintain the intravascular volume with an expanded vascular capacitance.

Contractility is manipulated through the use of inotropic medications. These include direct β-adrenergic agonists (e.g., epinephrine and dobutamine) and phosphodiesterase inhibitors (e.g., milrinone). Calcium chloride infusions may also be of benefit in cardiogenic shock, particularly in younger children who seem to derive a substantial contractility benefit from increased extracellular calcium concentrations. Similar to afterload reduction, these medications can be titrated based on invasive measurements or clinical improvements in cardiac output. Limiting factors for β-adrenergic agonists include increased myocardial oxygen consumption, tachycardia and other arrhythmias, and undesired increases of SVR or PVR. Limiting factors for phosphodiesterase inhibitors include hypotension (i.e., excessive afterload reduction and/or vasodilation), which may occur secondary to increased drug accumulation in the setting of renal dysfunction.

A more recent trend in the management of patients with established cardiomyopathies (i.e., chronically compensated cardiogenic shock) deemphasizes the use of β-adrenergic agonists due to obligate increases of myocardial oxygen consumption and cellular level changes leading to further cardiomyocyte dysfunction. In fact, some of these patients benefit from long-term use of highly selective β_1-adrenergic antagonists in combination with afterload reduction and diuretics, once they are no longer in acute cardiogenic shock.

Assuming that the heart rate is appropriate, the therapeutic strategies for cardiogenic shock focus on optimizing stroke volume by treatments that optimize preload, reduce afterload, and increase contractility. In addition, decreasing metabolic demand, when feasible, can improve the balance between oxygen delivery and demand. Cautious fluid boluses or passive leg raise is used to test if the patient is preload responsive. If the patient has signs of edema and/or documented increased cardiac preload (e.g., by echocardiography), then diuretics are indicated.

In patients with cardiac dysfunction and low stroke volume, afterload-reducing agents can improve stroke volume with little effect on the patient's mean arterial pressure. Unlike inotropic agents, afterload-reducing agents improve stroke volume while simultaneously reducing myocardial oxygen demand. Inotropic agents may be needed in the short term, but they increase myocardial oxygen demand and increase the risk of tachyarrhythmias; depending on the agent, they may increase afterload. Patients with chronic heart failure may benefit from long-term use of highly selective β_1-adrenergic antagonists in combination with afterload reduction and diuretics.

Distributive shock: Treatment for pure distributive shock includes restoration of vascular tone and intravascular volume expansion. Since the primary cardiovascular mechanism in distributive shock is pathologic vasodilation, the use of vasoactive medications that restore vascular tone is appropriate as a primary supportive therapy. These include norepinephrine and phenylephrine infusions. Epinephrine infusions can also be used, but its β_1-adrenergic agonist effect on the myocardium may not be necessary and could be detrimental. Furthermore, epinephrine's β_2-adrenergic agonist action on vascular smooth muscle may further reduce vascular tone. Intramuscular epinephrine injections are typically used at the onset of anaphylactic shock and help reduce bronchospasm through its β_2-adrenergic effects as well as inhibit mediator release from mast cells. The need for intravascular volume expansion is predicated on the concept that pathologic vasodilation leads to increase vascular capacitance leading to relative hypovolemia with decreased venous return. Adjunctive therapies for distributive shock secondary to anaphylaxis include corticosteroids and antihistamines. Older therapies that are garnering re-discussion include angiotensin II (ATII) for its favorable vasopressor effects through vasoconstriction and increased aldosterone production. Recent studies have shown the positive benefits of ATII in distributive shock by decreasing the total dose of catecholamines needed. Endogenous

Treatment for pure distributive shock includes restoration of vascular tone and intravascular volume expansion. Epinephrine is used to treat anaphylactic shock, but norepinephrine is preferred for spinal shock.

angiotensin II is created by the angiotensin-converting enzyme (ACE) converting angiotensin I to II. In states of stress, there can be reduced ACE activity and therefore a decreased production of angiotensin II, thus accounting for the benefit of an ATII infusion. Additional studies have found a benefit of ATII when prescribing continuous renal replacement therapy (CRRT). The benefit in this setting reflects an improved ability to remove fluid while avoiding hypotension and decreasing renal oxygen consumption when compared to catecholamines alone.

Septic shock As mentioned earlier in this chapter, septic shock is characterized by all three major classifications of shock: hypovolemic, cardiogenic, and distributive shock. Accordingly, all of the aforementioned supportive therapies and therapeutic endpoints are potentially applicable to the management of septic shock. The clinical challenge lies in the recognition that the degree to which any one of these three forms of shock is present in a given patient can be highly variable and may change over time. Aggressive intravascular support, however, is generally accepted as a primary supportive therapy for all patients with septic shock, at least in developed countries where there is access to advanced care and technologies. This recommendation is supported by historical data demonstrating improved outcomes for children with septic shock that received >40 mL/kg of fluid administration during the first hour of presentation. In the setting of aggressive fluid management, the clinical challenge then becomes whether the patient should be supported primarily for cardiogenic shock, distributive shock, or some combination of the two. Physical exam in combination with CVP response to a fluid challenge and echocardiography are typically sufficient data to make this decision. For certain patients, insertion of a PAC may provide further useful information on which to base therapeutic decisions. Specific recommendations and guidelines for supportive cardiovascular therapy in pediatric septic shock were published by a task force composed of pediatric critical care practitioners sponsored by the American College of Critical Care Medicine and the Society of Critical Care Medicine. The recommendations include serial examination for signs of intravascular fluid overload during volume loading in order to avoid iatrogenic injury from volume overload. Additionally, there are a subset of patients who require continued aggressive fluid resuscitation due to ongoing losses. It is prudent to ensure that acute fluid balance goals are achieved.

Historically, high-dose, short-term corticosteroids were used for patients with septic shock, but when this approach was subjected to formal, randomized trials, they were proven to not be of benefit and perhaps were detrimental. However, the use of corticosteroids in septic shock has been reconsidered and coupled with the concepts of longer term therapy, lower doses, and "relative adrenal insufficiency." The latter is based on an ACTH stimulation test followed by serial measurements of serum cortisol levels. Previously, relative adrenal insufficiency was defined as a serum cortisol concentration <9 μg/dL following ACTH stimulation. Using these criteria for initiation of corticosteroid replacement therapy, a significant survival benefit was demonstrated in adult patients treated with a combination of hydrocortisone and fludrocortisone. However, a subsequent trial based on a similar strategy failed to show a survival benefit secondary to adjunctive hydrocortisone. Further, a recent consensus conference was unable to generate a universally accepted definition of relative adrenal insufficiency.

There have been two recent large trials testing the efficacy of adjunctive corticosteroids in adults with septic shock, neither of which used ACTH stimulation and cortisol measurements. The ADRENAL trial randomized 3800 septic patients in Australia and New Zealand to hydrocortisone or placebo and

found no difference in all cause mortality at 90 days, although those treated with hydrocortisone had faster resolution of shock. The APROCCHSS trial randomized 1241 patients to hydrocortisone plus fludrocortisone or placebo. Those receiving hydrocortisone plus fludrocortisone had a 90-day mortality rate of 43%, whereas those in the placebo group had a 90-day mortality rate of 49% ($p = 0.03$; NNT ≅ 17).

Pediatric sepsis guidelines notwithstanding, there are no analogous large clinical trials involving children to inform the use of adjunctive corticosteroids in pediatric septic shock. A meta-analysis of available trials did not demonstrate a survival benefit. Observational studies have also failed to show efficacy, and some suggest harm. This important question regarding the role of adjunctive corticosteroids for pediatric septic shock can only be answered via a large randomized trial, which is currently in the planning stages.

Ultimate progress in further advancing therapeutic strategies in both adults and children with septic shock may be predicated on the development of stratification strategies. Because septic shock is a heterogeneous syndrome, rather than a distinct disease, several subclasses of patients with septic shock are likely to exist based on the host response to an infectious challenge. Unfortunately, clinical trials for septic shock fail to address this heterogeneity. Current translational research efforts in pediatric septic shock are directly addressing this challenge of heterogeneity by systematically deriving septic shock stratification tools based on biomarkers and gene expression signatures. The ultimate goals of these stratification strategies is to more rationally conduct clinical trials in more biologically homogeneous populations and to better inform individual patient management.

Septic shock may be characterized by components of all three major classifications of shock: hypovolemic, cardiogenic, and distributive shock. Initial aggressive intravascular support is generally accepted as a primary supportive therapy for all patients with septic shock, at least in developed countries. Fluid refractory septic patients are more likely to have myocardial dysfunction with or without abnormal vascular tone.

Because septic shock is a heterogeneous syndrome, rather than a distinct disease, several subclasses of patients with septic shock are likely to exist based on the patients' host response to an infectious challenge. Clinical sepsis trials fail to address this heterogeneity, but current translational research is directly addressing this challenge of heterogeneity by systematically deriving septic shock stratification tools based on biomarkers and gene expression signatures. These trials may help identify, for example, which patients may benefit from corticosteroid therapy, a therapy that remains quite controversial.

Review Questions

1. The statement that best describes physiologic alterations observed in shock is:
   A. Cardiogenic shock is more often the result of diastolic dysfunction than systolic dysfunction.
   B. Distributive shock is characterized by reduced cardiac output and pathologic vasodilation.
   C. Hemorrhagic shock produces an acute reduction in oxygen carrying capacity and may be complicated by multiple organ dysfunction syndrome.
   D. Increasing the partial pressure of oxygen often results in the greatest increase in oxygen carrying capacity.
   E. Septic shock often displays a predictable hemodynamic profile across multiple hosts.

2. Shock at the cellular level may be characterized by:
   A. Compromised oxidative phosphorylation and rapid accumulation of cytosolic ATP
   B. Decreased activation of nuclear factor-κB activation
   C. Failure of neutrophil apoptosis causing prolonged tissue inflammation
   D. Low levels of poly(ADP-ribose) polymerase-1 activity leading to ATP depletion
   E. Overproduction of nitric oxide leading to pathologic vasoconstriction

3. The most correct statement regarding the monitoring of therapeutic interventions during shock is that:
   A. Decreased $S_{cv}O_2$ can be indicative of inadequate oxygen delivery or decreased oxygen consumption, while increases of $S_{cv}O_2$ in response to therapy can be indicative of effective therapy for shock.

B. Due to the variable clinical examination findings in shock, serial examinations have been supplanted by more objective measures of shock such as lactate and mixed venous oxygen saturation determinations.
C. Insertion of a pulmonary artery catheter is often necessary early in the treatment of septic shock.
D. Mixed venous oxygen saturation is best measured from a pulmonary artery catheter with the tip in the pulmonary artery or alternatively by a central venous line with the tip at the inferior portion of the right atrium.
E. Serial examinations and serial measurements of mixed venous or central venous oxygen saturation and lactate can serve as a guide for the severity, evolution, and resolution of shock.

4. A 6-year-old, 20 kg boy recently diagnosed with acute lymphocytic leukemia is undergoing induction chemotherapy. He develops fever and is found to be neutropenic (absolute neutrophil count 410 cells/μL), anemic (hemoglobin 8.1 gm/dL), and thrombocytopenic (platelet count 108,000/μL). In the clinic, he is cool distally, has poor pulses, and has a delayed capillary refill of 5 seconds. He develops sustained tachycardia to 180 beats per minute and has a blood pressure of 85/67 mm Hg. He is given a 400 mL bolus of normal saline and is transferred to the PICU. Upon PICU arrival, he is agitated, is poorly perfused, and remains tachycardic (167 beats per minute). His blood pressure is 94/78 mm Hg. Central venous blood obtained from a Broviac catheter (tip located at the superior portion of the right atrium) reveals a central venous oxygen saturation of 55% and a lactate of 3.4 mmol/L. He has made minimal urine since his admission. The most correct statement regarding his management is which of the following?
A. An additional 20 mL/kg normal saline should be administered while awaiting the arrival of packed red blood cells for transfusion.
B. Further volume resuscitation should be withheld pending results of a STAT echocardiogram.
C. No further volume resuscitation is required. He requires rapid initiation of inotropic support.
D. No further volume resuscitation is required. He requires rapid initiation of vasopressor support.
E. No further volume resuscitation is required. He requires rapid initiation of afterload reduction.

5. A 17-year-old adolescent boy is transferred from an outlying facility to the PICU for treatment of refractory pneumonia. He had a 10-day viral prodrome consisting of low-grade fever, progressive fatigue, and dyspnea. His initial chest radiograph revealed bilateral basilar infiltrates. His current exam reveals tachypnea (34 breaths per minute), tachycardia (132 beats per minute), and a blood pressure of 110/91 mm Hg. He is cold distally and has a capillary refill time of 5 seconds. He is anxious and complains of chest pain. Repeat chest radiograph reveals diffuse bilateral infiltrates and cardiomegaly. Bedside ultrasound demonstrates no pericardial or pleural effusion, dilated ventricles, and depressed contractility. His oxygen saturation is 98% on 2 liters oxygen via nasal cannula. An arterial lactate is 7.8 mmol/L. Which of the following statements best describes the etiology and treatment of this patient?
A. He has become fluid overloaded from overzealous fluid administration and requires aggressive diuresis.

B. His pneumonia is now complicated by ARDS and septic shock. He requires endotracheal intubation and initiation of epinephrine at 0.1 mcg/kg/minute.
C. Myocarditis should be strongly suspected. He should undergo rapid endotracheal intubation and have an epinephrine infusion initiated at 0.5 mcg/kg/minute.
D. Myocarditis should be strongly suspected. Furosemide should be administered and a dopamine infusion initiated at 20 mcg/kg/minute.
E. Myocarditis should be strongly suspected. Milrinone should be initiated at 0.5 mcg/kg/minute while awaiting echocardiography.

6. A 16-year-old female develops fever, rigors, diffuse erythema, and syncope. In the emergency department, she is found to have tachycardia (162 beats per minute) and a blood pressure of 98/35 mm Hg. She is warm distally and has a capillary refill time of less than 1 second. She is anxious and complains of diffuse myalgias. She again becomes syncopal when sitting up. She is placed in the Trendelenburg position and is given three 20 mL/kg normal saline boluses over 1 hour. Her perfusion is unchanged and repeat blood pressure is 100/22 mm Hg. She is given an additional 20 mL/kg fluid bolus upon arrival to the PICU and has a central venous catheter placed. ST changes are noted on the bedside cardiac monitor. Which of the following statements best describes the etiology and treatment of this patient?
   A. She has cardiogenic shock complicating sepsis and requires the institution of a milrinone infusion.
   B. She has a distributive type of septic shock and requires more fluid resuscitation.
   C. She has a distributive type of septic shock and requires the initiation of a high-dose dopamine infusion.
   D. She has a distributive type of septic shock and requires the rapid institution of a vasopressor such as norepinephrine.
   E. She has overwhelming hypodynamic sepsis and requires the institution of an epinephrine infusion.

7. The correct statement regarding acid-base status and shock is that:
   A. A bicarbonate infusion following volume resuscitation is often necessary to correct systemic acidosis.
   B. Increased anion gap metabolic acidosis is often due to bicarbonate loss.
   C. Initial measurements of arterial blood gases and lactate, in the setting of shock, are highly predictive of outcome.
   D. Multiple factors, other than insufficient oxygen delivery, can affect acid-base status and include liver dysfunction and infusions of normal saline.
   E. Shock can lead to increased dependence on aerobic metabolism, which results in overproduction of pyruvate.

Answers

1. C
2. C
3. E
4. A
5. E
6. D
7. D

Suggested Readings

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Disorders of Cardiac Rhythm

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Contents

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Learning Objectives

- Summarize the physiology of the cardiac action potential.
- Summarize how antiarrhythmic medications alter cardiac conduction.
- Discuss the various mechanisms that generate tachyarrhythmias (increased automaticity, reentrant tachycardias, and triggered activity).
- Describe how to identify and treat common pediatric tachyarrhythmias.
- Describe the causes and treatment of bradycardia.
- Describe basic pacemaker functionality.
- Summarize the natural history and treatment of common pediatric rhythm disorders.

18.1 Fundamental Electrophysiology

Cardiac cells maintain a net negative charge, resulting in a transmembrane gradient that allows for action potential generation.

A fundamental understanding of cardiac electrophysiology allows the clinician to manipulate cardiac conduction in the clinical setting. The normal myocardium has the ability to generate, contract in response to, and propagate an action potential. Cardiac cells maintain an ion gradient across the cell membrane with an overall negative intracellular charge. This *transmembrane gradient* facilitates ion flow and the generation of the action potential, which is the driving force for cardiac activity (Fig. 18.1). Cardiac cells maintain high intracellular potassium (140 mM/L) and low intracellular sodium (10 mM/L) concentrations as the major source of the transmembrane gradient. Low intracytoplasmic calcium levels (10^{-4} mM/L) also contribute to the resting equilibrium potential. These values have clinical implications. For example, a rise of the extracellular potassium concentration (hyperkalemia) decreases the cardiac transmembrane potential, which, if severe, can ultimately lead to asystole. Conversely, bolus intravenous calcium administration augments the calcium component of the transmembrane gradient, which counteracts some of the negative electrophysiologic effects that are induced by abnormally high serum potassium concentrations.

The low cytoplasmic calcium concentration also highlights the remarkable energy-based pumping function of the cardiac cell to maintain an ~10,000-fold calcium concentration gradient between the inside and outside of the cell.

Low intracellular Na and Ca with high intracellular K concentrations maintain the transmembrane gradient.

Cardiac cells generate the action potential largely by maintaining low intracellular Na^+ and Ca^{++} concentrations, together with a high intracellular K^+ concentration.

Sinus node tissue usually demonstrates the fastest phase 4 depolarization, thereby controlling the heart rate. Sinus node and other automatic tissue increase their phase 4 depolarization rate in response to heat (fever) and catecholamine stimulation. Similar effects may be seen in nodal tissue with the removal of parasympathetic input.

The cardiac action potential begins with rapid, phase 0 depolarization. Phase 0 activity results from rapid Na^+ influx (I_{Na}) through newly opened sodium channels and produces a transient decrease (positive deflection) of the transmembrane potential. Depolarization of a single cell stimulates opening of sodium channels on neighboring cells, producing a spreading cur-

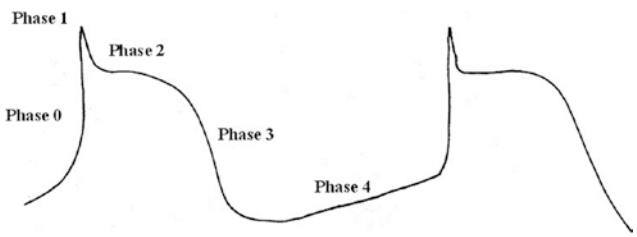


Fig. 18.1 Action potential of a cardiac myocyte: Phase 0, rapid depolarization caused by rapid sodium influx; phase 1, early phase of repolarization caused by rapid inactivation of sodium channels and opening of potassium channels; phase 2, plateau phase of repolarization characterized by slow calcium influx; phase 3, late repolarization with calcium channels closing and an outward transmembrane flow of potassium down its concentration gradient to assist in restoring the negative intracellular charge and return to resting potential; phase 4, early depolarization

rent across the entire heart. Per convention, the depolarization wave is read as a positive reflection as it moves toward a surface electrode on a standard electrocardiogram; conversely, a downward reflection is recorded as the depolarization wave moves away from a surface electrocardiogram lead. Following contraction, the myocyte must repolarize in order to undergo subsequent conduction/contraction cycles. Repolarization comprises phases 1–3 of the action potential and is mediated via a number of ion channels with complex and yet to be fully elucidated cellular and molecular interactions. Unlike nerve cells, cardiac cells have a prolonged action potential (thus delaying repolarization) as is represented by the flattened plateau phase 2 and slope of phase 3. Delayed phase 2 repolarization is mediated by the balance of inward calcium (I_{Ca}) and outward potassium flow (I_K), with the cell returning to its resting potential at the conclusion of phase 3. In general, cardiac cells are unable to conduct a new impulse until they have completed phase 3 repolarization. The duration of phases 1–3 of the action potential approximates the *refractory period* of the tissue. Cardiac cells differ in their rate of phase 4 depolarization. In the normal state, sinus node tissue demonstrates the fastest rate of phase 4 depolarization, thereby providing innate pacemaker function.

Antiarrhythmic drugs typically affect specific ion channels and therefore alter specific portions of the action potential. For example, by binding to channel proteins and inhibiting sodium ion influx, class I drugs slow the rate of phase 0 depolarization and slow cardiac conduction velocity. In the 1970s, E. M. Vaughan Williams proposed an antiarrhythmic drug classification based mainly on empiric experimental data. This classification system remains relevant today and is presented in Table 18.1.

Antiarrhythmic medications affect specific portions of the action potential in order to alter cardiac conduction and intrinsic pacemaker activity. Medication choice is often targeted to achieve a particular response, depending on the arrhythmia being treated.

An exhaustive discussion of antiarrhythmic pharmacology is beyond the scope of this text. However, individual agents will be discussed in the context of specific arrhythmias and their treatment.

Table 18.1 Vaughan Williams drug classification

Class	Action	Drug examples
I	Sodium channel blockers	
IA	Prolong the action potential duration	Procainamide, disopyramide
IB	Shorten (or do not change) action potential duration	Lidocaine, phenytoin
IC	Mildly prolong the action potential	Flecainide, propafenone
II	Beta-adrenergic blockers	Atenolol, propranolol, etc.
III	Potassium channel efflux blockers (prolong the action potential by inhibiting phase 4 depolarization)	Amiodarone, sotalol
IV	Calcium channel blockers	Diltiazem, verapamil
V	Miscellaneous commonly used agents	Adenosine, digoxin

18.2 General Arrhythmia Mechanisms

Most *tachyarrhythmias* can be classified as being caused by reentry, increased automaticity, or triggered activity.

Three general mechanisms produce most tachyarrhythmias: (1) *reentry*, which involves circular, self-propagating rhythm cycles; (2) *increased automaticity*, produced by abnormal impulse generations; and (3) *triggered activity*, arising due to "afterdepolarizations" in diseased heart muscle. Specific tachyarrhythmias are largely named/identified based on where in the heart these mechanisms arise (see Fig. 18.2).

For example, a reentrant circuit confined to the atria may produce atrial flutter, whereas a reentrant circuit located in the ventricle produces a ventricular tachycardia. Similarly, atrial-level triggered activity has been described in some patients with multifocal atrial tachycardia, which may be well tolerated in the short term, but can lead to cardiomyopathy when chronic. Conversely, triggered activity arising in the ventricle may produce torsades de pointes, a potentially fatal rhythm associated with the congenital long QT syndrome.

18.2.1 Reentry Disorders

Reentry is the most frequent mechanism of tachyarrhythmias and is defined as a cardiac impulse generating subsequent depolarizations in a sequential, predictable manner.

Reentry is the most frequent mechanism producing tachyarrhythmias. *Reentrant circuits* are responsible for a variety of supraventricular tachyarrhythmias (SVTs) including bypass tract-mediated tachycardias, atrial flutter, and atrioventricular nodal reentrant tachycardias (AVNRT). Reentrant phenomena are also commonly associated with ventricular tachycardia in the adult, where ischemia and infarction may produce variations in local conduction properties. Reentry can be defined as a cardiac impulse that generates subsequent depolarizations in a sequential, predictable manner. *During reentry, a single heartbeat regenerates itself*. For this to occur, a variety of conditions must be met. First, a nonuniform conduction pathway must be present that typically differs from normal in both (i) conduction velocity and (ii) refractory period. Second, to initiate the reentrant circuit, a premature impulse must arrive at a time when the more slowly repolarizing arm of the circuit is refractory. Finally, the specific geometry and timing characteristics of the circuit must be precise in order for the arrhythmia to be sustainable. Any manipulation of circuit conduction characteristics (e.g., slowing conduction with a class

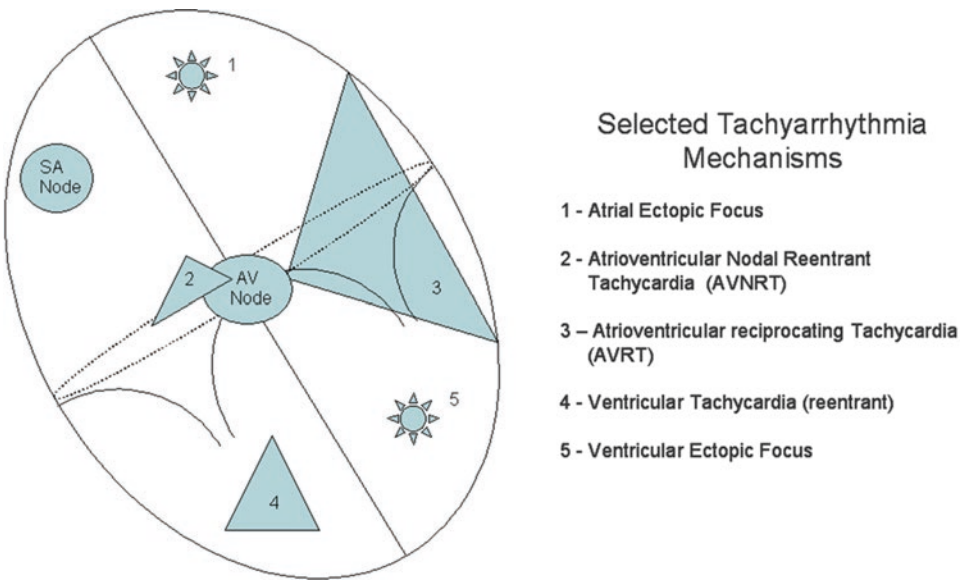


Fig. 18.2 Selected tachyarrhythmia mechanisms

I agent or slowing repolarization with a class III agent) may render the circuit unsustainable and thereby prevent or terminate an arrhythmic event.

Clinically observable or described characteristics of an arrhythmia may offer some insight as to the underlying mechanism. Reentrant circuits are either "on" or "off." Reentrant supraventricular tachycardia (SVT) begins suddenly (in paroxysms) typically with no warning or prodromal symptoms. Additionally, since reentrant circuits are "hardwired," heart rates tend to vary little from one event to another. Patients generally experience similar, increasingly familiar symptoms from event to event. A teenager with episodes of SVT with a documented heart rate of 189 bpm during one event will likely have nearly the same heart rate during their next event. Duration of their event may vary, but quality and severity of their tachycardia-related symptoms typically do not. This predictability is an important factor for risk assessment and overall patient management. Response to treatment may also aid in differentiating reentrant disorders from those due to abnormal automaticity. Reentrant tachycardias often terminate in response to any brief interruption of the regenerating circuit. For example, electrical cardioversion interrupts nearly any reentrant rhythm. Adenosine, which temporarily interrupts AV nodal conduction, is frequently effective in terminating atrioventricular or atrioventricular nodal reentrant tachycardias, which are commonly seen in infants and adolescents, respectively. In contrast, disorders of automaticity are typically refractory to cardioversion or adenosine administration.

Reentrant SVT begins suddenly and most often has a fixed heart rate.

Most children with normal hearts tolerate brief periods of SVT without profound hemodynamic compromise; however, SVT may not be tolerated in children with congenital heart disease, or when unrecognized and prolonged in young infants. These symptomatic infants or children may require emergent cardioversion and subsequent hemodynamic support.

While most brief SVT episodes are well tolerated, prolonged SVT or SVT in a patient with congenital heart disease may become hemodynamically significant.

18.2.2 Disorders of Automaticity

Automatic arrhythmias may be more variable, and therefore less clinically predictable, than reentrant arrhythmias. Automatic rhythms result from increased and often variable rates of depolarization in specific areas of the heart referred to as *ectopic foci*. Ectopic foci can occur in the atria, great veins near their atrial insertion points, near the AV node, or in the ventricles. Similar to sinus node tissue, ectopic foci typically increase their rate of phase 4 depolarization in response to increasing temperature, catecholamine stress, or stimulant exposure. When the rate of an ectopic focus is similar to that of the sinus node, only occasional extra or early beats may be seen. Patients may or may not sense these ectopic beats. With increasing rates, ectopic foci may overtake the sinus node and drive a tachycardia. Automatic tachycardias often demonstrate gradual rate increases (warm up) and may be prolonged (incessant), lasting for multiple hours in a day. Incessant atrial tachycardias are often, but not always, identified by the presence of abnormal P-waves on a 12-lead ECG. Identification and treatment of chronic atrial tachycardia is important, since this type of arrhythmia has been associated with the development of tachycardia-associated cardiomyopathy and end-stage heart failure.

18.2.3 Triggered Tachycardias

As noted, triggered tachycardias result from abnormal *afterdepolarizations* that occur following normal cardiac depolarization. These abnormal afterdepolarizations typically occur during phase 2, 3, or early in phase 4 of the action

Triggered tachycardias are due to abnormal afterdepolarizations.

potential. When they occur, they interrupt normal repolarization. Afterdepolarizations with subsequent triggered tachyarrhythmias (e.g., torsades de pointes) often occur in conditions where the action potential is prolonged such as with prolonged QT syndrome, digitalis toxicity, and generalized critical illness.

18.2.4 Rapid Evaluation of Acute Arrhythmia

Findings from a rhythm strip should be rapidly verified and identified as hemodynamically significant or insignificant based on auscultation and pulse assessment.

Ectopic atrial tachycardia should be looked for and ruled out in any child presenting with a newly diagnosed dilated cardiomyopathy. A 12-lead ECG should be quickly performed, when possible, in all children being evaluated for a tachycardia.

When evaluating an acute arrhythmia, the practitioner must first evaluate the clinical status of the patient. Visual inspection alone is often sufficient to establish the state of consciousness and evaluate a patient's level of distress or discomfort. Brief examination of the extremities reveals the character of distal pulses and provides an assessment of overall perfusion. Auscultation and pulse assessment are critically important parts of patient evaluation and are necessary to confirm cardiac monitor and rhythm strip findings. Motor activity (shivering or tremor), chest physiotherapy, lead displacement, and monitor dysfunction can all lead to false arrhythmia alarms. Importantly, when evaluating a newly identified arrhythmia, one should strive to obtain a 12-lead electrocardiogram (ECG) as soon as patient stability allows. A multi-lead ECG provides a much more detailed and standardized analysis of a rhythm disorder, as compared with a single rhythm strip generated from a patient's bedside monitor. Documentation with a 12-lead ECG should be emphasized as a mandatory step for identification and treatment of most rhythm disorders observed on a patient's bedside monitor.

18.3 Specific Arrhythmias and Their Treatment

18.3.1 Bradycardia

Bradycardia is a frequent occurrence in the critical care unit and can have myriad causes (see ► Box 18.1).

Bradycardia is frequently encountered in critically ill children as a secondary and reversible response to excessive vagal stimulus, hypoxia, or myocardial hypoperfusion. Bradycardia also can result from primary congenital conduction system abnormalities as well as a variety of surgical, immunologic, or pharmacologic insults to nodal or conductive tissue (see ► Box 18.1). The myocardium relies heavily upon aerobic metabolism, and pacemaker cells are exquisitely sensitive to the effects of hypoxemia. Intensivists must quickly identify, evaluate, and correct the myriad issues that can lead to acute hypoventilation, hypoxemia, and myocardial hypoperfusion in the intensive care unit. Acutely ill children quickly become bradycardic and may progress to full cardiac arrest if abnormal gas exchange is not rapidly addressed and corrected.

Box 18.1 Selected Causes of Bradycardia in Children

- Hypoxemia
- Hypothermia
- Hypotension (severe)
- Hyperkalemia
- Increased vagal tone (athletes, airway interventions, intracranial injury)
- Drug effects (β-blockers, digoxin, calcium channel blockers, clonidine, tricyclic antidepressants, etc.)
- Sinus bradycardia
- Sinus node dysfunction

- Congenital heart block
  (a) Anatomic with complex congenital heart disease (e.g., heterotaxy patients, L-transposition)
  (b) Immune-mediated (e.g., maternal lupus)
- Acquired AV block (surgical)
- Toxin exposure (e.g., carbon monoxide, snake venom, some plants)

Nodal cells are exquisitely sensitive to hypoxemia, which is the most common cause of bradycardia in children. Prompt airway evaluation and intervention prevents most cardiac arrests in children.

Vagal stimulation occurs in the ICU during such common procedures as endotracheal intubation and tracheal suctioning. Sinus bradycardia with marked sinus arrhythmia is commonly present in even mildly brain-injured children. It is important to recall that a state of autonomic imbalance exists in infancy; sympathetic innervation of the myocardium is functionally immature. Although the density of cardiac β-adrenergic receptors is high, β-receptor-adenylate cyclase coupling mechanisms are inefficient. Conversely, vagal innervation of the myocardium is complete and functional at birth. This leads to a state of parasympathetic dominance in early infancy and thus a propensity toward bradycardic events. Increased parasympathetic output also contributes to the infantile laryngeal reflex, which has been implicated as a cause of apnea and bradycardia seen in association with gastroesophageal reflux disease (GERD) and formula aspiration. Vagal-mediated acetylcholine release at the level of both the sinus and AV nodes affects pacemaker cells in a dual fashion, causing a hyperpolarization of cardiac tissue (a more negative intracellular baseline polarization) and a decrease of the slope (rate) of phase 4 depolarization. This combined effect greatly slows pacemaker function and may even cause a cessation of sinus node activity.

Atropine and glycopyrrolate can be used to attenuate vagal-mediated bradycardia, although epinephrine remains the PALS drug of choice in a bradycardic arrest requiring resuscitation.

Vagal-mediated bradycardia can be attenuated by the muscarinic receptor antagonists atropine and glycopyrrolate; the latter has the advantage of not causing any CNS side effects and can be given orally if needed for chronic suppression of increased vagal activity. Muscarinic antagonists prevent acetylcholine from binding to cholinergic receptor cells in the heart, smooth muscle, gland cells, and elsewhere. Atropine premedication is often recommended prior to performing laryngoscopy or tracheal intubation in infants and small children to prevent reflex bradycardia and to decrease the production of airway secretions. However, prospective data suggest that this widespread practice may not be necessary or effective for all pediatric patients. Atropine is generally dosed at 0.02 mg/kg intravenously with a minimal dose of 0.1 mg and a maximal adult bolus dose of 1 mg. The minimal dose is recommended to reduce the risk of a paradoxical bradycardic response that can occur with smaller doses. Intravenous atropine administration may produce pupillary dilatation, which is an important consideration when assessing a patient's neurological status following a resuscitative event. In the adult, maximal pupillary dilatation occurs after total atropine doses >2 mg. In children, atropine has an approximate half-life of 2–3 h. Atropine use in pediatrics is most appropriate for the treatment of symptomatic bradycardia with suspected parasympathetic excess or for treatment of anticholinesterase or other similar poisonings.

Atropine is one treatment option for vagally mediated bradycardia. The dose is 0.02 mg/kg with a minimum and maximum of 0.1 mg and 1 mg, respectively. The minimal dose is recommended to reduce the risk of a paradoxical bradycardic response that can occur with smaller doses.

Isoproterenol is a nonselective β-adrenergic agonist which leads to increased heart rate and contractility with no α-adrenergic affinity.

Non-vagal causes of bradycardia are less frequent in children. In general, low heart rates are well tolerated in otherwise healthy children, particularly if there is a gradual onset of bradycardia. In contrast, the sudden onset of complete AV block may not be hemodynamically tolerated; in this setting, atropine use may be attempted. Adrenergic agonists may also provide benefit by increasing nodal conduction and the automaticity of accessory pacemaker tissue. Remember that resuscitation guidelines recommend epinephrine as the first-line agent for symptomatic bradycardia in children. Historically, many intensivists used isoproterenol (Isuprel™) as an effective agent to increase sinus node rate and AV nodal conductivity. Isoproterenol is a nonselective β-adrenergic agonist with no affinity for α-adrenergic receptors. This unopposed β-adrenergic stimulation increases the heart rate and can temporarily stabilize patients prior to pacemaker insertion. Due to its strong β_2-adrenergic effects producing systemic vasodilation, intravascular volume status should be optimized concurrent with its use. Aggressive β_2 stimulation is contraindicated in children with left ventricular outflow tract obstruction (LVOTO) (e.g., subaortic stenosis, hypertrophic cardiomyopathy), as it may increase the outflow gradient by decreasing aortic diastolic pressure, and these effects can decrease diastolic myocardial perfusion. Additionally, pure β-adrenergic agonists should be avoided in children with lesions associated with low diastolic pressures (e.g., systemic-pulmonary shunts, aortic regurgitation), as they further decrease diastolic pressure and coronary filling. Pediatric isoproterenol dosing is generally titrated between 0.05 and 0.5 mcg/kg/min; higher infusion rates up to 2 mcg/kg/min have been reported.

External pacing capability is built into most cardiac defibrillators but should only be used as a temporizing method.

External transcutaneous pacing is a reliable method to treat acute bradycardia related to pacemaker dysfunction or other acute conduction failure in any age patient. It is ineffective and not indicated for treatment of the terminal asystole following unsuccessful resuscitation efforts in a non-rhythm-related cardiac arrest. External pacing capability is built into most cardiac defibrillators, but transthoracic pacing should only be used as a temporizing method.

Symptomatic bradycardia that is unresponsive to pharmacologic intervention requires pacemaker support. Temporary pacing is indicated until a permanent pacemaker can be placed. Temporary pacing can be accomplished by external transcutaneous or transvenous techniques in most patients. Transesophageal left atrial pacing is another option when an intact conduction system is present. External pacing capability is built into most cardiac defibrillators used in the hospital environment. *External pacing* is a widely available, potentially uncomfortable, but lifesaving procedure that should be considered in selected settings with profound bradycardia. External pacing can temporize bradycardia seen with some drug ingestions, permanent pacemaker failures, or profound electrolyte disturbances. Importantly, external pacing has not been shown to be helpful, and is therefore not indicated, for the treatment of terminal asystole seen during an unsuccessful resuscitation originating from a non-arrhythmic origin. External pacing can be performed in all ages, although full thickness burns have been reported with its prolonged use in a premature infant. External pacing is generally performed using multipurpose pacer/defibrillation pads commonly used with modern hospital-based defibrillators. Following pad placement, the operator dials in an age-appropriate desired heart rate, which is generally 10–20 bpm higher than the patient's normal resting heart rate. Pacer output (milliamps) is sequentially increased until ventricular capture occurs, which is identified by the loss of the intrinsic rhythm and the onset of a "spike and wave" pattern showing a wide complex QRS pattern with associated T-waves. Capture must always be confirmed by the presence of an arterial waveform or palpable pulse. Sedation and analgesia should be offered to the awake patient, which may necessitate airway support. In most situations, external pacing should be considered a bridge to either transvenous or permanent pacer placement.

Transesophageal and transvenous pacing for infants and small children is typically performed following consultation with an electrophysiologist or other cardiology subspecialist. Transvenous pacing wires can be connected to standard bedside external pacemaker generators. Successful transvenous pacer placement has been reported in newborns and young children using all central venous access sites (internal jugular, subclavian, or femoral vein) often utilizing fluoroscopic guidance. In the adult-sized adolescent, the cephalic vein can be used with the catheter advanced blindly into the right heart guided by ECG evidence of signal capture. Alternatively, ultrasound has been reported as a useful tool to guide correct catheter position. Transesophageal pacing is a safe and technically straightforward method of pacing both pediatric and adult patients when there is intact atrial to ventricular conduction. The esophagus abuts the left atrium and allows the recording of a high-amplitude atrial electrogram with reliable atrial pacing. Ventricular pacing via the esophagus is possible but is less reliable and often requires an uncomfortable amount of current to assure pacing capture. Electrophysiologists also use esophageal recordings to diagnose and treat atrial tachyarrhythmias. Temporary epicardial pacer wires are also frequently placed during congenital heart surgery. Atrial or esophageal leads can be directly connected and recorded on a standard 12-lead ECG to directly measure the atrial electrogram. Atrial electrograms clearly identify P-wave activity and can help distinguish between rhythms such as atrial flutter, AV reentrant tachycardias, and junctional rhythms. Reentrant SVT and atrial flutter can be effectively treated by overdrive (burst) atrial pacing. Transesophageal atrial pacing carries some risk of inducing ventricular fibrillation, so equipment to provide defibrillation shocks should always be readily available when using this technique.

While transesophageal atrial pacing can be useful, it does carry the risk of inducing ventricular fibrillation, so a defibrillator should always be available.

Permanent pacemaker implantation is indicated for children with a variety of rhythm disorders. Infants may develop complete heart block in association with structural heart disease (e.g., L-transposition) or in the setting of maternal systemic lupus erythematosus (SLE). Maternal autoantibodies to SSA/Ro and SSB/La proteins can cross the placenta and destroy fetal conductive tissue. The resultant third-degree AV block is permanent and leads to a high incidence of fetal congestive heart failure (*hydrops fetalis*). Infants may tolerate third-degree heart block if they have an adequate ventricular escape rate, but neonates are typically symptomatic when the ventricular rate is below 55–60 bpm. Pacemaker implantation is indicated for symptom relief in such infants. Increasing global experience and pacer availability led to the publication of standardized indications for pacemaker placement in children. As an example, pacer placement is a class I recommendation for infants with congenital third-degree heart block with a ventricular escape rate of less than 50–55 bpm. Evidence also supports permanent pacer implantation in symptomatic infants with higher heart rates, those with associated structural heart disease, a wide complex QRS escape pattern, or pause-dependent ventricular tachycardia. Permanent pacemakers are typically placed transvenously in the older child and adults utilizing local anesthesia to access the cephalic or subclavian veins. A pacer generator is then placed into a subcutaneous pocket in the infraclavicular region. Size limitations prevent the use of this technique in infants and smaller children who therefore require surgically placed epicardial wires and subcostal generator placement. Full operative sternotomy may be indicated for more complex placements. Correct pacemaker operation is assured intraoperatively with full electronic interrogation of the device's sensing and pacing functionality. Data supports the use of antibiotic prophylaxis for 24 hours surrounding permanent pacer implantation using an anti-staphy-

Class I recommendations for congenital complete heart block include a ventricular escape rhythm of less than 50 bpm, symptomatic infants, infants with long pauses, or infants with wide complex QRS escape patterns.

Permanent pacemakers are typically placed in infants and children with congenital or acquired heart block. Modern devices are complex and require electronic interrogation if a malfunction is suspected.

lococcal agent. Once implanted, modern pacemaker function can be examined by direct telemetry or by indirect, trans-telephonic, monitoring. Pacer telemetry allows the clinician to examine the patient's innate rhythm, see a record of arrhythmic events, test sensing and pacing thresholds, and determine remaining battery strength and lifespan.

Placement of temporary atrial and ventricular epicardial pacing wires is standard procedure after complex cardiac repairs. Postoperative inflammation, edema, electrolyte abnormalities, and direct injury to the conducting system place the postoperative child at significant risk for arrhythmia. Interventions to control postoperative arrhythmias include maintenance of physiologic and metabolic parameters, antiarrhythmic agents, and at times temporary cardiac pacing.

A complete review of cardiac pacing is covered elsewhere in the text. However, critical care practitioners should be familiar with temporary cardiac pacemaker functionality. Modern pacemakers are becoming increasingly sophisticated as to their ability to sense the intrinsic heart rhythm, pace multiple cardiac chambers, and respond to a patient's variable cardiac demand. The North American Society of Pacing and Electrophysiology endorsed a uniform code to delineate pacer functions. There are five coded positions, of which the first three are most important in postoperative temporary cardiac pacing (see ► Box 18.2).

Pacemaker functionality is described using a 5-letter pacing code system where the first letter designates the chamber that is paced (A, atrial; V, ventricular; or D, dual chamber). The second letter designates whether or not a chamber's activity is sensed (0, no sensing; A, atrially sensed; V, ventricular sensing; D, dual chamber sensing). The third letter designates the response to a sensed beat (0, no response; I, pacing is inhibited; T, pacing is triggered; or D, dual response based upon programmed characteristics). The fourth and fifth letters are less commonly used in the PICU and designate programmable rate functions and the presence of anti-tachycardia/arrhythmia settings.

The generic 5-letter pacing code is ordered as follows: chamber paced, chamber sensed, response to sensing, rate modulation, and multisite pacing.

Box 18.2 Pacer Terminology[a]

I. *Chamber(s) paced*
   - 0 – None
   - A – Atria is paced
   - V – Ventricle is paced (right ventricle)
   - D – Dual, both the atria and the ventricle are paced

II. *Chamber(s) sensed*
   - 0 – None
   - A – Atrial
   - V – Ventricular
   - D – Dual chamber sensing

III. *Response to sensing*
   - 0 – None
   - I – Pacing is inhibited (i.e., pacing is not necessary due to spontaneous chamber activity)
   - T – Triggered (e.g., atrial sensing triggers ventricular pacing)
   - D – Dual (e.g., atrial sensing triggers ventricular pacing, unless there is an appropriately timed, conducted ventricular response)

IV. *Fourth letter designates programmable functions, such as rate responsiveness*

V. *Fifth letter designates anti-tachycardia functionality (e.g., burst pacing, defibrillation, etc.)*

[a]Pacemaker settings are designated by a lettered system. Typically used settings include AAI (atrial demand pacing), VVI (ventricular demand), or DDD (dual chamber demand) settings

Temporary pacemaker settings are typically described using the first three of the five standard categories; letters IV and V describe additional features used in more sophisticated, permanently implanted devices. For example, V00 describes asynchronous ventricular pacing. In this mode, the ventricle is paced at a set, predetermined rate regardless of innate ventricular activity. With V00 pacing, th ventricle is paced (V), and no sensing of ventricular activity is performed (0), so there is no response to sensing (0). Asynchronous ventricular pacing is rarely used outside of an emergency setting as it is inefficient and carries the theoretical risk of inducing dangerous ventricular arrhythmias should a pacer spike occur during repolarization (an "R on T" phenomenon). Ventricular demand pacing (VVI) represents a better option to assure a minimal ventricular rate. In VVI pacing, the ventricle is paced (V), ventricular activity is monitored (V), and, if the patient's intrinsic rate is equal to or higher than the set rate, pacer activity is inhibited (I). Ventricular demand (VVI) pacing safely assures a minimal ventricular rate and avoids pacing the patient unnecessarily. Dual chamber demand pacing (DDD) is typically used with transvenously placed permanent devices. DDD pacing requires the presence of bipolar (sensing and pacing) leads in both the atria and the ventricle. DDD pacing assures a minimum heart rate, allows for sequential AV pacing, and, by sensing intrinsic chamber activity, avoids unnecessary pacing. Intensivists should remember to consult their cardiology colleagues for pacemaker interrogation if device malfunction or arrhythmic problems are suspected.

18.4 Common Atrial Tachyarrhythmias

18.4.1 Sinus Tachycardia

Sinus tachycardia is most commonly confirmed in children identified with a narrow complex tachyarrhythmia. Clinicians must remember to define a tachycardia considering age-appropriate heart rate norms and the clinical context of the patient. Published "normal" heart rate ranges are often based on data from healthy resting children, which is not relevant in the child with acute pain, anxiety, or fever. Sinus rates of 150 bpm are relatively unremarkable in the agitated infant but are likely significant in the older child or adolescent. Sinus node and other "automatic" tissues increase their rate of phase 4 depolarization in response to stimuli such as endogenous or administered catecholamines, elevated temperature, decreased vagal nerve activity (vagolysis), and thyroid hormone excess (thyrotoxicosis). Sinus tachycardia is most commonly a secondary manifestation of some other clinical stressor, as opposed to a primary pathology. Endogenous catecholamine stimuli are nearly universal in the intensive care setting where hypotension, fever, anemia, heart failure, anxiety, and pain are frequently encountered. When confronted with a narrow complex tachycardia, the intensivist must confirm a sinus origin and then treat the underlying condition producing the adrenergic stress. Differentiating a sinus tachycardia from other forms of narrow complex tachycardia is not always an easy task. The degree of heart rate elevation is the first clue. Maximal sinus rates decline with age and can be *approximated* by the simple formula of 220 – patient age (in years).

18.4.2 Supraventricular Tachycardias

A. Automatic mechanisms.
   - Sinus tachycardia.
   - Ectopic atrial tachycardias.

B. Atrial reentry.
   - Atrial fibrillation.
   - Atrial flutter.

C. Atrioventricular reciprocating tachycardias (atrioventricular reentry).
   - Atrioventricular reciprocating tachycardia (AVRT).
     (a) Concealed pathways (normal baseline ECG).
     (b) WPW (preexcitation on baseline ECG).
     (c) Orthodromic SVT – ventricular activation via the His-Purkinje system (typical narrow complex SVT).
     (d) Antidromic SVT – ventricular activation via accessory pathway during SVT (often produces a wide complex SVT).
   - Atrioventricular nodal reciprocating reentrant tachycardia (AVNRT).

D. Atrial triggered activity.
   - Chaotic atrial tachycardia.
   - Digoxin toxicity.

The lower limit for sinus tachycardia is age dependent and therefore should be considered in the context of the child's age. Maximal sinus rates decline with age and are approximately 220 bpm minus the patient's age in years. Rates higher than this are suggestive, but not diagnostic, of a non-sinus tachycardia. For example, sinus rates may be higher than this estimate in infants with high fever, but this is not common. Unusually fast heart rates should trigger an analysis of the ECG to rule out the presence of a tachyarrhythmia.

The catecholamine stress response in combination with a high fever can lead to high sinus rates in severely ill infants and young children (sinus rates as high as 240 bpm have been documented, although this is rare). A heart rate >200 bpm in an infant (perhaps >160 bpm in the older child) should generally be suspected to arise from a non-sinus mechanism and prompt the clinician to exam an ECG. Children with a variety of atrial and reentrant tachycardias often have heart rates in the 200–300 bpm range, or higher. Clinical characteristics differentiating a sinus tachycardia from other rhythms are summarized in Table 18.2.

18.4.3 Paroxysmal SVT

Paroxysmal SVT occurs when an accessory pathway is present and allows for abnormal atrioventricular conduction.

As previously mentioned, most supraventricular tachycardias in children originate from reentrant mechanisms involving *accessory pathways*. In large part, the electrophysiologic properties of specific reentrant tachycardias are determined by the location and conductive properties of the specific pathway involved. In infants and young children, accessory tissues commonly bridge the fibrous skeleton of the heart, electrically connecting the atria and ventricles at an additional site separate from the AV node. Atrioventricular conduction normally occurs *only* at the AV node/His bundle, as depicted in Fig. 18.3. Accessory pathways often do not support anterograde (forward) conduction during normal sinus beats. These pathways produce no abnormalities on the baseline surface electrocardiogram and are therefore said to be *concealed*. Alternatively, some accessory tissues can conduct in an anterograde (forward) manner during a baseline sinus rhythm, leading to delta waves on the baseline electrocardiogram (delta waves are diagnostic of Wolff-Parkinson-White (WPW) syndrome; see below).

Paroxysmal supraventricular tachycardia is seen in all age groups. SVT in infants and small children typically results from an accessory atrioventricular pathway in the reentrant circuit. This form of SVT is referred to as an atrioventricular reciprocating tachycardia (AVRT). AVRTs typically show a narrow QRS complex with rates of 200–300 bpm (or faster). Figure 18.4 is an example of an AVRT in an infant. Note the R-P interval with downward ori-

Table 18.2 Differentiating sinus tachycardia from other arrhythmias

Sinus tachycardia	Non-sinus rhythms
Rates less than age appropriate max (often <200 bpm)	Often >200 bpm
Clear P-waves present, 1:1 relationship with subsequent QRS complex (regular P-R relationship)	P-waves may be absent, have multiple morphologies, or occur after the QRS complex (retrograde R-P relationship)
Normal P-wave axis (0–90°)	Often inferior oriented or variable P-wave axis
Gradual onset, rate warms and slows with clinical interventions (volume expansion, sedation, etc.)	Reentrant SVT has an abrupt onset and termination (paroxysmal)
Typically demonstrates some rate variability. Often phasic, undulating rate changes	Reentrant SVT demonstrates little or no rate variability Ectopic tachycardias may show highly irregular, chaotic rates
Narrow complex QRS	VT or SVT with aberrant conduction typically shows a wide complex QRS. Ventricular origin is confirmed if atrioventricular disassociation can be demonstrated. A wide complex tachycardia should be assumed to be of ventricular origin until proven otherwise
Normal central venous waveform	Cannon A-waves or irregular CVP waveform

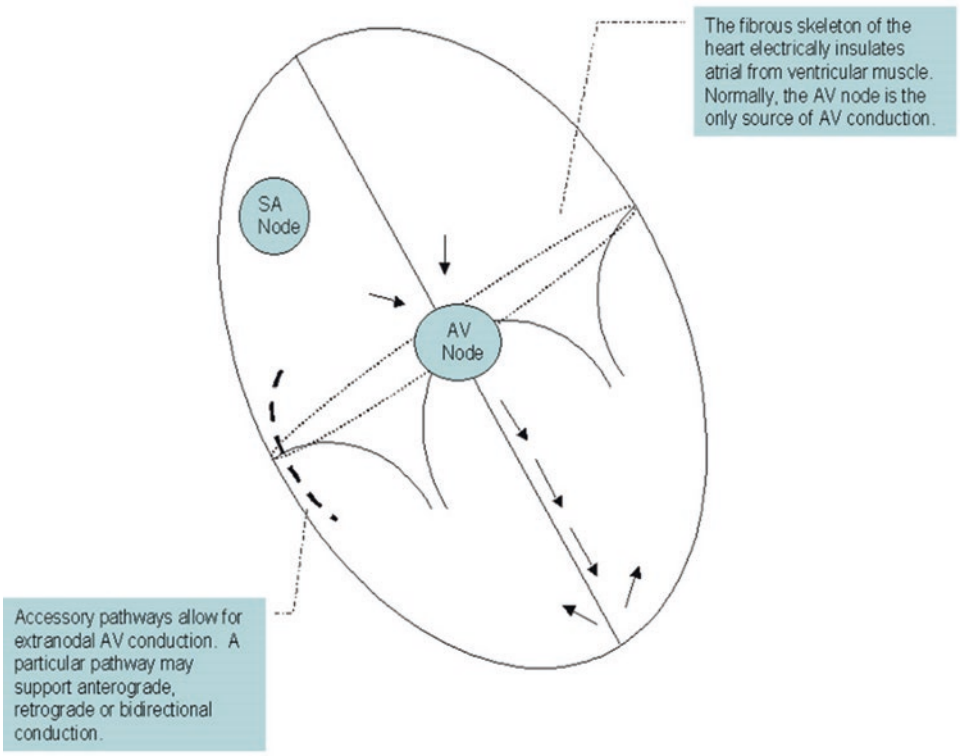


Fig. 18.3 Normal AV conduction (arrows) and accessory pathway (dashed line) that has the potential to allow extranodal AV conduction

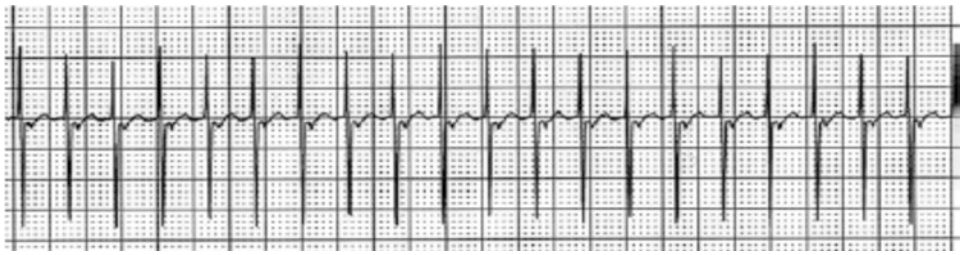


Fig. 18.4 Rhythm strip demonstrating AV reciprocating tachycardia (AVRT). SVT in infants frequently utilizes congenital accessory pathways that electrically connect the atria and ventricles distant from the AV node. These accessory pathways act as one limb of a reentrant circuit during AVRT. Accessory tissue often regresses during infancy, with many infants "outgrowing" their tachycardia. Conversely, some children develop accessory pathways in or near the AV node during late childhood and adolescence and develop episodes of AVNRT

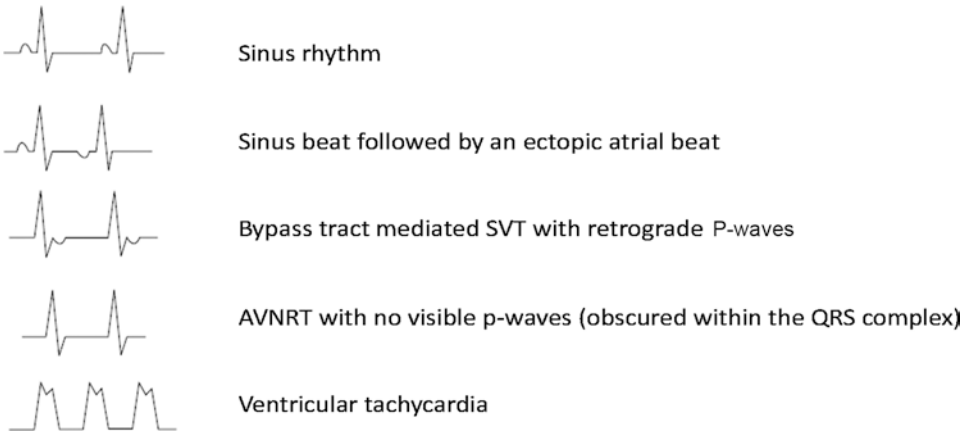


Fig. 18.5 Idealized P-wave morphology in selected arrhythmias

ented P-waves produced in lead II by retrograde activation of the atria. This is an example of an *orthodromic* tachycardia, defined when the reentrant circuit conducts in the normal direction through the AV node and His bundle. The atria are then activated in a retrograde manner with V-A conduction through the accessory pathway, producing the negative P-wave orientation. Since the ventricles are activated through the normal conduction pathways, a narrow QRS complex results.

Paroxysmal SVT occurs when an accessory pathway is present and allows for abnormal atrioventricular conduction. The most common form of paroxysmal SVT in infants and young children involves an accessory pathway outside of the AV node, whereas in older children and adolescents, it involves a recurrent pathway near or within the AV node itself.

SVT occurring in older children or adolescents is more likely to arise from a reentrant pathway near or within the AV node itself – an atrioventricular nodal reentrant tachycardia (AVNRT). The 12-lead surface ECG can often give some clue as to the type of SVT in a particular patient; in a hemodynamically stable patient, this should be carefully reviewed prior to administering any treatment. P-wave identification is often a crucial step for diagnosis. AVRT often produces clear retrograde P-waves with a 1:1 ventricular-atrial relationship and a consistent R-P interval. In contrast, multiple P-wave morphologies with inconsistent P-R relationships will be seen with ectopic atrial tachycardias, which do not utilize a reentrant circuit. P-waves may not be visible during an AVNRT, since they are often simultaneous with, and obscured by, the QRS complex. Figure 18.5 demonstrates idealized ECG appearances for several different tachyarrhythmias.

18.4.4 Wolff-Parkinson-White Syndrome (WPW)

WPW is an example of an *antidromic* AVRT where depolarization moves from the ventricle to the atria through the AV node. Children with WPW have an accessory pathway that supports forward (anterograde) conduction from the

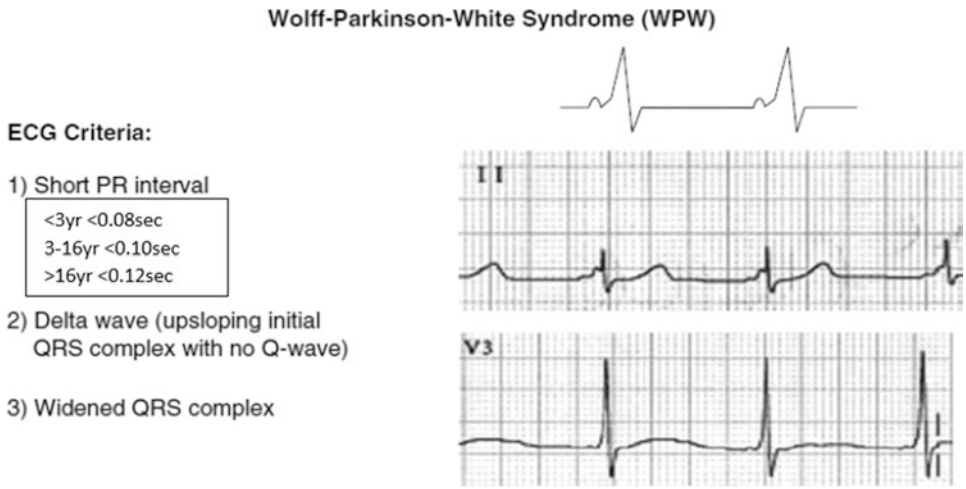
atria to the ventricle during a normal sinus rhythm. Unlike normal conduction via the AV node, there is *no* pause of atrial to ventricular conduction along the accessory pathway. This leads to early activation of the ventricle, thereby shortening the P-R interval and producing the delta wave and widened QRS complex characteristic of the WPW syndrome. Note that the absence of a q-wave is also characteristic of preexcitation. In some patients, accessory tissue can support very fast conduction velocities. These patients are potentially at risk for sudden cardiac death should they develop fast atrial rhythms such as atrial fibrillation or atrial flutter. Normally, AV nodal conduction delay protects the ventricle from excessively fast atrial stimulation. However, if an accessory pathway is present, and it is capable of fast conduction, very high atrial rates may be transmitted directly through to the ventricle and potentially induce lethal ventricular fibrillation. This mechanism is thought to be responsible for a low, but not negligible, risk of sudden cardiac death in some patients with WPW. Children with preexcitation (WPW) should be referred to a pediatric cardiologist for risk assessment and a complete cardiovascular evaluation. ECG criteria for WPW are seen in ◘ Fig. 18.6.

WPW occurs when there is early activation of the ventricles (seen as a delta wave or shortened P-R interval on ECG). Some accessory pathways may allow fast atrial to ventricular conduction, thereby putting the child at risk for ventricular fibrillation and sudden cardiac death should they develop an atrial tachyarrhythmia. Therefore, all children with preexcitation (WPW) should be evaluated by a pediatric cardiologist.

18.4.5 Wide Complex SVTs

Most SVTs produce narrow QRS complexes, but this is not absolute. Forward (antidromic) conduction along accessory pathways, the presence of multiple accessory pathways, and rate-dependent conduction blocks are some of the mechanisms that can lead to wide QRS complex reentrant SVTs. In these settings, it can be very difficult to differentiate an SVT from a ventricular tachycardia. In the stable patient, debate over the specific diagnosis can often be prolonged and esoteric. However, when confronted with a hemodynamically unstable patient, clinicians should assume a wide complex rhythm is of ventricular origin. Per standard resuscitation protocols, *a hemodynamically unstable patient with an organized tachycardia thought to be of cardiac origin (of either narrow or wide complex morphology) should be promptly treated with synchronized cardioversion using 0.5–1 J/kg*. If the patient is pulseless, then asynchronous settings should be used and the patient should be defibrillated using 2 J/kg.

While some wide complex SVTs may be hemodynamically stable, an unstable patient should be promptly treated with 0.5–1 J/kg of synchronized cardioversion.



◘ **Fig. 18.6** Wolff-Parkinson-White syndrome (WPW)

18.4.6 SVT Treatment

Paroxysmal SVT is typically well tolerated in otherwise normal children. This is important to remember when evaluating a child for a newly identified tachycardia. In the outpatient setting, children often have vague complaints of palpitations for years prior to suffering a sustained episode that is captured on an electrocardiogram. In most cases, patients should be taught to think of SVT as a nuisance, rather than a danger. SVT can, however, be life-threatening in specific situations. For example, infants lack the ability to fully communicate and may suffer an unrecognized tachycardia for many hours or even days prior to developing recognized signs of illness. These infants come to medical attention when they develop an acute rate-related cardiomyopathy and congestive heart failure. Immediate and long-term rate control is essential in these infants in order to maintain and improve their cardiac function.

Children with congenital heart disease, underlying cardiomyopathy, or an excessively fast tachycardia may also develop rapid hemodynamic collapse during an SVT event and require emergent care. Note that infants with otherwise normal cardiac structure and concealed or WPW pathways have a high incidence of spontaneous resolution during the first year of life. Thus, it is common for infants to "outgrow" their tachycardia. Conversely, adolescents may "grow into" their AVNRT with increasing episodes or medication dependence during late childhood and the teenage years. Treatment options for SVT are relatively vast with the tenor of clinical intervention based upon the severity of a child's symptoms.

Vagal maneuvers can be very effective in terminating reentrant SVT by altering conduction properties of the AV node. In infants, applying a bag of iced saline induces a diving reflex. Older children can be taught to perform the Valsalva maneuver.

Most types of reentrant SVT in children utilize AV nodal tissue as part of the reentry circuit. Since reentry requires precise timing to sustain itself, any alteration of AV nodal conduction properties or refractoriness can render the circuit unsustainable and prevent or abort an SVT event. *Vagal maneuvers* can be very effective in terminating reentrant SVT; these maneuvers lead to AV nodal cell hyperpolarization, thereby slowing conduction in that arm of the reentrant circuit. Beta-adrenergic blockade and digoxin are thought to act similarly in terms of altering AV node function. The Valsalva maneuver, when performed in the supine position and held for 20s, has been shown to break over half (53%) of AVRT and one-third of AVNRT-associated tachycardia in adult patients undergoing electrophysiologic study. A school-age child can be taught to perform the Valsalva maneuver by blowing on a clamped straw or the tip of their thumb, continuing for the required 15–20 seconds. Other common vagal maneuvers include holding iced water to a child's face (thereby inducing a diving reflex). The ice bag technique, where an ice water-containing bag is held over the entire forehead and face, while avoiding obstructing the nose and mouth, for up to 15 s is recommended as especially effective for infants and children when performed appropriately. Due to their simplicity, safety, and relative efficacy, vagal maneuvers should be attempted as initial therapy for most children presenting with paroxysmal SVT.

Vagal maneuvers fail to break SVT roughly 50% of the time. Adenosine administration is generally recommended as the next intervention of choice for most children with SVT. Adenosine is a naturally occurring nucleoside that binds to specific G-protein-coupled receptors located in the atria, AV node, and ventricular tissue. Adenosine receptor activation secondarily opens potassium channels, leading to cellular hyperpolarization. Furthermore, by inhibiting adenylate cyclase, adenosine inhibits L-type calcium channels, which reduces conduction velocity. Reduced cAMP also reduces the slope of phase 4 in pacemaker cells, reducing their pacemaker rate. Bolus adenosine administration in most individuals produces a short period of complete heart block

and transient (<5 sec) asystole. This brief interruption is sufficient to abort most types of reentrant SVT that rely on the AV node as a component of their circuit. In vascular smooth muscle, adenosine administration stimulates G-protein activation of adenylate cyclase, which causes systemic vasodilation with a resultant baroreceptor-mediated sympathetic response. Many patients feel transient chest pain, likely secondary to the profound bradycardia/brief asystole leading to myocardial ischemia. Sympathetic activation can be quite marked and may speed or otherwise alter conduction properties of a reentrant circuit or automatic tissue. Thus, adenosine administration poses at least a theoretical risk of inducing ventricular fibrillation in some patients, thereby mandating continuous ECG monitoring and a bedside defibrillator whenever adenosine is used.

Adenosine is administered as a starting dose of 0.1 mg/kg (maximum, 6 mg) and is best given by a two-syringe, rapid bolus technique. This is performed by rapidly pushing the drug through the largest, most central vein possible, followed immediately with a large volume flush of normal saline. Adenosine may be administered via the intraosseous route. A continuous, multi-lead ECG recording should be obtained surrounding adenosine injection in order to obtain maximal diagnostic information. If ineffective, the dose of adenosine can be doubled to 0.2 mg/kg (maximum, 12 mg) and repeated. Adenosine has a half-life of seconds, thus drug accumulation does not occur.

Adenosine, when given by rapid intravenous bolus, interrupts AV nodal conduction, thereby interrupting reentrant SVT and restoring sinus rhythm. Adenosine administration is the treatment of choice for the hemodynamically stable patient with SVT not responsive to vagal maneuvers. If adenosine is used to attempt to terminate an SVT rhythm, it should be done in bolus form, given quickly as close to the heart as possible, and monitored with a continuous ECG rhythm strip during administration since adenosine administration can be diagnostic by examining the cardiac rhythm during the pause of AV nodal conduction.

Successful sinus conversion of a narrow complex SVT essentially confirms the diagnosis of either an AVRT or AVNRT. When unsuccessful, careful review of the electrocardiogram often provides clues as to the mechanism of the tachycardia. Junctional ectopic tachycardia or some ventricular tachycardias may continue unchanged following bolus adenosine dosing. Alternatively, adenosine-induced complete heart block may allow for a clear ECG tracing of atrial activity and prove the presence of ectopic atrial activity, flutter waves, or other similar mechanisms (Fig. 18.7).

Clinicians must remember to continually monitor hemodynamic status during SVT by following mental status, palpation of pulses, and blood pressure measurements. Patients may be placed supine or in Trendelenburg position to augment venous return and maximize their cardiac output. As stated previously, synchronized cardioversion with 0.5–1 J/kg should be used in any unstable patient with an organized narrow or wide complex tachycardia, especially when immediate pharmacologic intervention is not possible.

Recurrent evaluation of the patient with stable SVT is crucial, as they may become hemodynamically unstable with a more prolonged episode.

Suppressive pharmacologic therapy is indicated for most children who have frequent or prolonged bouts of SVT. Digoxin and beta-adrenergic blockade are most commonly employed for SVT control in children. Calcium channel blockers, such as verapamil, can also be very effective but can have profound (**even lethal!**) negative inotropic effects in infants and young children. For this reason, calcium channel blockers are generally contraindicated for treatment of SVT in this age group. Many pediatric cardiologists choose to treat infants and young children with digoxin, a digitalis glycoside that produces a variety of electrophysiologic effects. Digoxin inhibits a sodium-potassium ATPase,

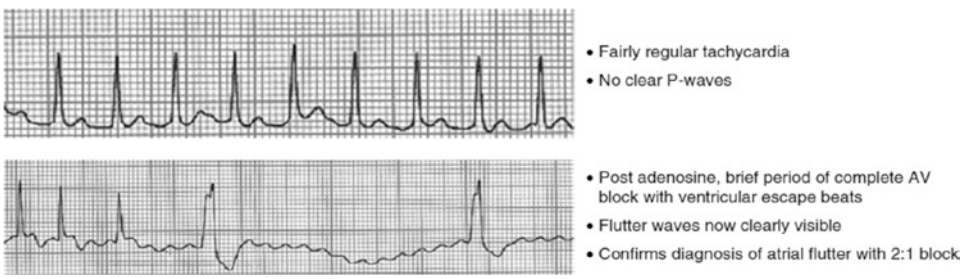


Fig. 18.7 Diagnostic use of adenosine revealing atrial flutter

leading to an increase in the intracellular sodium concentration. This, in turn, stimulates a sodium-calcium exchange mechanism that raises the intracellular calcium concentration. Increased intramyocardial Ca^{++} produces a positive inotropic effect, which is beneficial in low cardiac output states. As an antiarrhythmic agent, digoxin has potent effects at the AV node, where it leads to nodal cell hyperpolarization and slowed conduction. This vagomimetic effect directly alters the timing in a reentrant circuit, which may render it nonfunctional. It should be noted that digoxin and verapamil are *contraindicated* in the setting of WPW syndrome due to the risk of accelerating anterograde conduction along the accessory pathway. Accelerated conduction over an accessory connection may increase the risk of a rapid ventricular response during atrial fibrillation and potentiate the risk for inducing lethal ventricular fibrillation. For this reason, a beta-blocker is the initial drug of choice for treatment of WPW-associated SVT.

Digoxin is frequently used for the chronic treatment of SVT in infants and small children, but it is contraindicated with WPW, as it may accelerate conduction along accessory pathways. Digoxin has complex pharmacology with a narrow therapeutic index and a high degree of tissue binding as well as important drug interactions requiring careful monitoring of drug concentrations.

Digoxin has a long history of safe and effective use in the pediatric age group. Toxicity is rare but can be lethal. Oral digoxin has a slow initial rate of distribution, with peak serum levels achieved after 30–90 min during chronic administration. Digoxin is widely distributed, especially into skeletal and cardiac muscle, which results in a high volume of distribution. Most digoxin is eliminated unchanged in the urine with an elimination half-life that varies with age, ranging from 20 to 40 h; the long half-life is due to the high degree of tissue binding. Dosing should be adjusted in patients with impaired or immature renal function and in those receiving a variety of other commonly used drugs (e.g., amiodarone, erythromycin). Loading (digitalizing) doses are often employed in the first 12–24 h of therapy to overcome the large volume of distribution and more quickly achieve therapeutic levels. Alternatively, maintenance dosing can be initiated with the expectation of achieving steady-state concentrations after approximately 5 days of therapy. Digoxin may be administered once or twice daily. The drug has a narrow therapeutic window, with goal serum values generally between 1 and 2 ng/mL. Signs of toxicity include anorexia, vomiting, visual disturbances (blurred or yellow vision), atrioventricular block, and other atrial and ventricular arrhythmias. Hypokalemia, hypomagnesemia, and hypercalcemia can potentiate the arrhythmic potential during digoxin toxicity; these electrolytes should be measured and corrected as needed. Serious intoxications can be treated with anti-digoxin Fab antibodies.

β-Adrenergic antagonists are considered first-line therapy for a variety of atrial and ventricular arrhythmias. β-Blockade reduces the sinus node rate, decreases automaticity of ectopic pacemakers, slows conduction in the atria and AV node, and increases the functional refractory period of the AV node. Cardiac β_1-adrenergic receptors mediate inotropic and conduction effects. β_2 receptors are also located to a lesser extent in the atria and ventricles but primarily reduce tone in bronchial and vascular smooth muscle. A variety of β-adrenergic antagonists are currently available for clinical use. These vary in their receptor specificity, lipid solubility, and receptor agonist potential. Nonselective agents block both β_1 and β_2 receptors, whereas cardioselective agents have proportionately higher β_1 receptor specificity, with little or no β_2 effect. Nonselective β-blockers may precipitate bronchospasm in asthmatic individuals and are relatively contraindicated in this group. Importantly, vast data supports the safe use of cardioselective β_1-adrenergic antagonists (e.g., atenolol, metoprolol, esmolol) in adults with asthma and COPD, where they were shown to be safe and not associated with worsening of pulmonary function. Lipid solubility and volume of distribution also vary between agents.

These pharmacologic properties alter the side effect profile of each drug. Agents with increased lipid solubility have relatively greater CNS penetration and may be more likely to induce fatigue or other CNS effects (antianxiety, depression, etc.).

Propranolol had widespread clinical use since the 1970s. Propranolol is a non-cardioselective agent available in a liquid form suitable for infant administration. It is generally administered at a dose of 2–6 mg/kg/day divided every 6–8 h. It is a highly effective antiarrhythmic agent with an additional quinidine-like membrane-stabilizing action. Propranolol is often a first-line agent for infants and young children with WPW, AVRT, or ectopic tachycardias. Individual responses vary, making dose titration necessary, guided by heart rate response and antiarrhythmic efficacy. Nonselective β-blockers have metabolic effects that can be significant in children. Endogenous epinephrine stimulates hepatic glycogenolysis and glucose mobilization in response to hypoglycemia. Nonselective β-blockade can blunt this response, leading to symptomatic hypoglycemia, such as in infants during gastrointestinal illness with impaired oral intake, or in diabetics with insulin shock.

Atenolol is often used in the older child or adolescent, typically at doses of 25–50 mg daily. Atenolol is a cardioselective agent with the added benefit of little CNS penetration. Esmolol is a parenteral cardioselective agent with a brief half-life (~8 min) and a peak onset of action within 10 min. Esmolol is a useful drug in the intensive care setting where rapid onset, short half-life, and titratability are desirable. Esmolol is typically administered using a loading dose of 100–500 mcg/kg, with subsequent infusion rates of 25–500 mcg/kg/min. Longer term esmolol administration can be associated with CNS symptoms (confusion, personality change, lethargy). Esmolol remains a good choice for control of adenosine-resistant SVT, with the infusion either leading to sinus conversion on its own or by altering conduction sufficiently to allow successful adenosine use. A number of other drugs can be used to treat SVT in specific situations (e.g., amiodarone, calcium channel blockers, sotalol, propafenone, etc.). These agents are best used in concert with cardiology consultation.

β-Adrenergic blockade is very effective and is commonly used for suppression of SVT in older children. β-Adrenergic blockade can be associated with hypoglycemia in younger patients, especially during a gastrointestinal illness. A cardiologist should be consulted regarding the selection and dose of the best agent to use in the management of SVT.

During cardiac catheterization, detailed electrophysiologic studies (EPS) can be performed to localize most accessory tissue and, once found, destroy it using radio frequency energy (RF ablation). This procedure is considered an effective, routine standard of care for the older patient with WPW, difficult to treat SVT, or for individuals who simply prefer to stop taking a daily medication. With increasing experience, RF ablation is becoming more of a routine therapy for older infants and children. EP studies are performed using several multielectrode catheters inserted transvenously into the heart to precisely map the location of ectopic foci or accessory conduction tissue. There is some risk of valve, myocardial, or conduction system injury, although such complications are fairly rare. Patient age, size, rhythm severity, and ease of pharmacologic control all weigh into the decision to undergo RF ablation. Catheter ablation can be offered to any age patient, although there is likely increased risk of complications for infants and small children. RF ablation is often not deemed to be necessary in children who may outgrow their rhythm disorder or in those who can be easily controlled with medication. Several successful case series have been reported involving infants and toddlers with life-threatening or pharmacologically resistant arrhythmias, and this should always be considered as a therapeutic option in an experienced center. Multicenter studies showed that RF ablation is ultimately curative for the vast majority of children, with success rates as high as 97% and few reported complications (AV block in 1.2% among nearly 3000 study participants).

Electrophysiology studies are becoming more routine in the pediatric population and can provide valuable diagnostic details as well as definitive treatment for the vast majority of reentrant SVT and WPW dysrhythmias, but cannot be performed in young infants.

18.4.7 Atrial Flutter

While more common in adults, atrial flutter can be seen postoperatively after repair of certain congenital heart defects, most notably repair of anomalous pulmonary venous return.

Atrial flutter is a relatively uncommon rhythm disorder in children. It is most often encountered in children following surgical correction of congenital heart disease, especially following repair of anomalous pulmonary venous return or other similar left-sided surgery. Late atrial arrhythmias are also common following the Fontan procedure. Atrial flutter results from a reentrant circuit that is confined to the atria. Classic ECG findings include rapid flutter waves (typical rates of 300–400 bpm) with a negative P-wave axis (downward P-waves in leads II, III and AVF). AV node conduction slows the ventricular response, often with every second or third flutter wave conducting through to the ventricle (◘ Fig. 18.7 atrial flutter with 2:1 block). It is often difficult to maintain good pharmacologic control of atrial flutter in children. Digoxin is often used to slow AV nodal conduction and limit the ventricular response. Cardioversion is often required to terminate atrial flutter or atrial fibrillation, with several important considerations. First, atrial thrombi need to be ruled out by echocardiogram to prevent systemic emboli following conversion to sinus rhythm. In the adult-sized patient, this usually requires the use of transesophageal echocardiography (TEE) to obtain images of sufficient quality. In small or thin children, transthoracic (routine) echocardiograms often provide adequate imaging and a TEE can be avoided. The second important consideration with reference to elective cardioversion is the potential for sinus arrest post conversion since chronic atrial flutter often produces transient sinus node dysfunction. This requires the ability to externally pace a child following successful electrical cardioversion pending sinus node recovery. This is easily accomplished with the use of adhesive pacing/defibrillation pads available with modern defibrillators.

18.4.8 Junctional Ectopic Tachycardia (JET)

JET is primarily a postoperative dysrhythmia resulting from increased automaticity within the His-Purkinje complex leading to gradual increase in heart rate with atrioventricular dissociation.

Almost exclusively a postoperative tachycardia, JET is caused by enhanced and abnormal automaticity of cells within the His-Purkinje complex. This automaticity arises from some perioperative insult and is a transient process, with JET beginning within a few hours of surgery that typically resolves within a week postoperatively. JET is often identified when the heart rate approaches 170 bpm and may gradually accelerate toward 250 bpm or higher. Treatment is typically necessary when rates are sustained at or above 180 bpm. JET is most commonly a narrow complex tachycardia but may widen in the presence of a bundle branch block. In this setting, it may be difficult to differentiate JET from a ventricular tachycardia. As JET is an automatic dysrhythmia, the rate typically accelerates in a gradual fashion and becomes evident as the JET focus begins to compete with the sinus mechanism. When JET and sinus rates are similar, the heart rate may appear to be irregular as the two mechanisms compete for heart rate control. As JET speeds up and supersedes the sinus rate, the HR often becomes regular again. JET arises below the level of the AV node and may or may not consistently conduct in a retrograde manner. If no P-waves are seen in the setting of postoperative tachycardia, an atrial electrogram can be obtained using temporary pacing wires, if present. To confirm JET with an atrial electrogram, one looks to confirm that ventricular activation (the QRS complex) precedes the onset of P-waves. As JET is an automatic arrhythmia, rates tend to "warm up and cool down" over time and can be influenced by the

patient's temperature, endogenous and exogenous catecholamines, and sedation administration in a similar manner to that of a sinus mechanism. The central venous pressure waveform can provide clear evidence as to the presence of JET by the demonstration of prominent "cannon A-waves."

Cannon A-waves occur when the atria contract against a closed tricuspid valve. During JET the heart rate originates below the level of the AV node, not in the SA node. As a result, there is a loss of the normal atrial-ventricular contraction sequence and a loss of the normal "atrial kick." In the normal heart, atrial contraction prior to ventricular systole helps fill the ventricle; this may account for 10–15% of ventricular filling and thus stroke volume. In the postoperative setting, diastolic dysfunction is often present with a requirement for higher ventricular filling pressures to support ventricular preload and cardiac output, which makes ventricular preload more dependent on the "atrial kick." For this reason, the loss of sequential AV conduction caused by a JET rhythm can be particularly hazardous in a postoperative patient already struggling with a low cardiac output state.

A warming-up period is seen with JET, with the heart rate slowly increasing. Cannon A-waves may be seen on the monitor as the atria contract against a closed tricuspid valve. Diagnosis can be definitively made via an atrial electrogram if atrial wires are present.

JET results from some perioperative insult and to some extent seems to be preventable by optimizing intraoperative anesthetic, bypass, and operative techniques. The perioperative use of magnesium sulfate, amiodarone and dexmedetomine have all been shown to decrease the postoperative incidence of JET. All of these agents have a role in the postoperative treatment of this tachyarrhythmia.

Treatment is twofold as attempts should be made to slow the JET rate and to restore AV synchrony (see box).

Treatment of JET

1. Slow automaticity
   - Correct metabolic and electrolyte abnormalities with particular attention to Mg+, Ca+, and K+.
   - Reduce excessive inotrope administration (hemodynamic instability often mandates continued use of some vasoactive agents).
   - Mild hypothermia to 35 °C aimed to slow automaticity.
   - Provide adequate sedation to minimize endogenous sympathetic drive. There is some evidence that dexmedetomidine may be a useful agent since it reduces centrally mediated sympathetic nervous system activation.
   - Antiarrhythmics: Amiodarone is the preferred antiarrhythmic, typically administered by continuous infusion. Bolus administration can cause acute hypotension; pacing may be required if drug-induced bradycardia occurs.
2. Restore AV synchrony (atrial kick) with temporary atrial pacing

Mainstays of JET treatment include decreasing catecholamine stimulation as much as possible, minimizing metabolic/electrolyte abnormalities, and overdrive pacing (if atrial leads are available). Amiodarone is the preferred antiarrhythmic treatment but should be given slowly to avoid hypotension.

Overdrive pacing – once the rate has been slowed sufficiently (often using an amiodarone infusion), atrial or AV sequential pacing above the JET rate should be attempted to restore AV synchrony.

A variety of other supraventricular tachycardias are seen in the intensive care setting. Ectopic atrial tachycardia, multifocal atrial tachycardia, and atrial fibrillation are relatively rare disorders that may be seen in children with underlying heart disease, rate-related cardiomyopathy, or following congenital heart surgery. Care should focus on basic resuscitation principles when caring for these children, maintaining appropriate hemodynamic and respiratory support.

18.4.9 Ventricular Ectopy and Tachycardia

Ventricular ectopy originates from specific foci. Unifocal ventricular ectopy is typically a benign finding in *otherwise healthy children with normal cardiac structure and function* and is not a harbinger of higher-grade arrhythmia. Premature contractions can arise in either the atria or ventricles. In general, wide complex beats (>0.14 s) are ventricular in origin but can be confused with atrial beats when there is aberrant conduction across forward conducting accessory pathways. Several criteria can help differentiate atrial from ventricular ectopy. PVCs are typically not conducted in a retrograde manner through the AV node into the atria. This leads to two potential phenomena – (i) a compensatory pause of the ventricular response following a PVC and (ii) the potential for fusion beats. Figure 18.8 shows frequent unifocal ventricular ectopic beats in a child with a normal heart; note the "compensatory pause" after each PVC. Ventricular premature contractions depolarize infra-nodal tissue, often rendering it refractory to the next sinus beat. Sinus atrial beats continue rhythmically and unabated (in the example below, approximately every 960 msec). Close examination of the T-waves may identify the presence of a superimposed P-wave.

Sinus P-waves occurring during the ventricular refractory period are not propagated through ventricular tissue, producing the classic "compensatory pause" seen in association with ventricular ectopy. The combination of the SA node maintaining its original pace and the compensatory pause causes the length of two cycles including the PVC to be equal to twice the length of the previous cycle (2 × RR). In contrast, atrial depolarizations resulting from a conducted atrial ectopic beat typically depolarize sinus nodal tissue. Once a premature atrial contraction is conducted through the sinus node, sinus nodal tissue immediately repolarizes and continues with its undisturbed intrinsic rate. Thus, premature atrial contractions generally produce an early beat immediately followed by a continuation of the background sinus rate and do not produce the compensatory pause seen in association with ventricular ectopy.

Ventricular rhythm disorders are uncommon in pediatrics, and a thorough work-up should be performed if suspected, along with cardiology consultation. Unifocal ventricular ectopy (PVC) is typically a benign finding in *otherwise healthy children with normal cardiac structure and function* and is not a harbinger of higher-grade arrhythmia.

Ventricular rhythm disorders are relatively rare in the pediatric population. Ventricular ectopy in the presence of myocarditis, structural heart disease, inherited channelopathy, postoperatively, or in association with a critical systemic illness (e.g., shock, CNS injury, inotropic infusion) often warrants a complete cardiovascular evaluation with subsequent pharmacologic or device intervention. Table 18.3 lists selected, relatively common causes of ventricular rhythm disorders in children. Chronic VT occurs mainly with inherited channelopathies, postoperatively or from a relatively short list of idiopathic ventricular rhythm disorders. Secondary causes of VT occur in children with otherwise normal hearts undergoing the acute stresses of critical illness. In this setting, therapy is based on treating the underlying condition while addressing such issues as electrolyte disturbances or limiting potential arrhythmogenic medications. Increasing frequency or multifocal ventricular ectopy may force the clinician to wean catecholamine support and may serve as a marker of unfavorable myocardial energetics. The onset of hemodynamically compromising acute ventricular tachycardia (VT) demands prompt resuscitative interventions, whereas slower forms of chronic

Hemodynamically significant ventricular tachycardia should be promptly treated with attempted defibrillation using 2 J/kg and increasing to 4 J/kg for subsequent attempts.

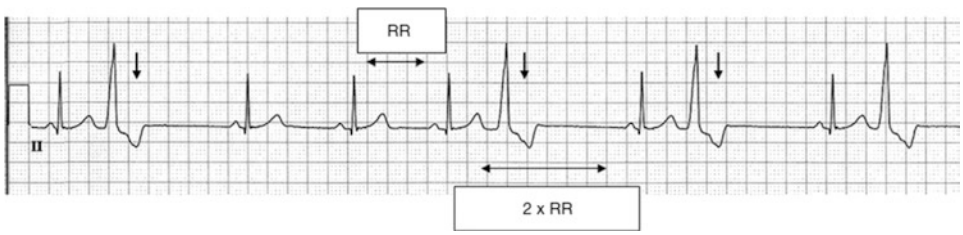


Fig. 18.8 Unifocal PVC with compensatory pause after each ventricular ectopic beat

Table 18.3 Common causes of ventricular ectopy/tachycardia

A. *Ventricular ectopic foci (automatic mechanism)*	
Benign ventricular ectopy	
Automatic ventricular tachycardia	
B. *Ventricular reentry*	
Postsurgical (circuit around a surgical scar)	
Postinfarction (chronic phase)	
C. *Ventricular triggered activity*	
Long QT-induced torsades de pointes	
Other inherited ion channelopathies (e.g., Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, others)	
Right ventricular outflow tract ventricular tachycardia (RVOT VT)	
Arrhythmogenic right ventricular dysplasia (ARVD)	
Adenosine-sensitive ventricular tachycardia	
Verapamil-sensitive ventricular tachycardia	
D. *Presence of an intracardiac catheter*	
Percutaneous intravenous catheters, PICC lines, dialysis catheters, etc., can migrate across the tricuspid valve and induce ventricular ectopy or sustained VT. This should be identified and corrected if present	
E. *Acute/secondary ventricular tachycardia (selected causes)*	
Acidosis	Anesthetics
Antiarrhythmic medications	Caffeine
Cardiac contusions	Cardiomyopathy (dilated, hypertrophic)
Catecholamines	Catheter irritation
Cocaine	Congenital heart surgery
Hyper- or hypokalemia	Hypocalcemia
Hypomagnesemia	Hypoxemia
Ischemia	Myocarditis
Pericarditis	Tricyclic antidepressants
Toxin exposures	Tumors (rhabdomyomas)

ventricular tachycardia may be hemodynamically tolerated. Once again, the clinician must perform a rapid patient assessment to decide on the appropriate tenor of intervention. Hemodynamically compromised or pulseless VT should always be treated with prompt defibrillation, per standard resuscitation protocols. For children, defibrillation energy is recommended to begin at 2 J/kg, increasing to 4 J/kg for subsequent shock attempts. Bolus epinephrine administration is recommended as an initial pharmacologic intervention for pulseless children unresponsive to three defibrillation attempts. Patients with VT and less severe hemodynamic compromise can be treated pharmacologically or with *synchronized* cardioversion using 0.5–1 J/kg. Current recommendations are to use the same energy dose with either a monophasic or biphasic defibrillator in the pediatric population since no outcome difference has been identified. Current defibrillators and AED devices use biphasic energy. In the pediatric critical care setting, three medications predominate for the treatment of ventricular tachy-

Monomorphic ventricular ectopy in a child with a normal heart may be a normal variant, caused by a benign ventricular ectopic focus. Conversely, ventricular ectopy in a child undergoing intensive care may be a marker of diseased myocardium at risk for ventricular arrhythmia. In the PICU, normal electrolytes should be assured, a transvalvular central venous catheter should be identified, and a complete cardiovascular assessment should be performed.

cardia. These include lidocaine, amiodarone, and magnesium sulfate. A wide variety of other agents may be encountered following electrophysiology consultation; for the purposes of this discussion, we will focus on these three medications.

18.4.10 Lidocaine

Lidocaine is a class IB antiarrhythmic primarily used for acute suppression/conversion of ventricular tachyarrhythmias.

Lidocaine is the classic agent widely used for decades for acute suppression/conversion of ventricular tachyarrhythmias. As a class IB drug, lidocaine blocks sodium channels leading to decreased membrane excitability, decreased conduction velocity, and slowed automaticity of ventricular tissue. Lidocaine has little effect on the QRS duration or QT interval. With these conduction effects, lidocaine is an effective treatment for ventricular tachycardia arising from a variety of origins. It may have a mild negative inotropic effect that should be kept in mind when used in the setting of left ventricular dysfunction. Lidocaine, when administered by rapid intravenous infusion, can cause seizure activity. Excessive plasma concentrations during prolonged intravenous infusion can produce tremor, speech changes, and CNS toxicity. Nystagmus is a typically described early marker of lidocaine toxicity. Lidocaine must be administered parenterally, as it undergoes extensive first-pass hepatic metabolism. It rapidly redistributes from the central compartment after bolus administration with a half-life of less than 10 min, thereby necessitating administration via a continuous infusion when used for continuous arrhythmia management. Pediatric dosing recommendations include a 1 mg/kg loading dose (may be repeated) followed by a continuous infusion of 20–50 mcg/kg/min. Lidocaine has a variable terminal elimination half-life (1.5–3 h); lower infusion rates are recommended for children with hepatic insufficiency or congestive heart failure. Lidocaine is a relatively safe drug with a vast history that remains part of routine resuscitation protocols. Other agents may be more effective in specific situations.

18.4.11 Amiodarone

Amiodarone is an antiarrhythmic acting at multiple ion channels useful for treating supraventricular and ventricular arrhythmias. Care should be taken when giving amiodarone due to its multiple mechanisms of action and large side effect profile.

Amiodarone is a drug with multiple class effects, useful for a variety of supraventricular and ventricular arrhythmias. Amiodarone is more effective than lidocaine when used in the setting of adult cardiac arrest. Amiodarone is an alternative to lidocaine during the resuscitation of children with pulseless VT/VF. Amiodarone has prominent class III (as well as class IB, II, and IV) effects that prolong the action potential, lengthen refractory periods, and slow AV node conduction and sinus node function. These multiple conduction changes combine to make amiodarone effective against most ventricular and supraventricular arrhythmias. It has an unusual pharmacokinetic profile with a high degree of tissue uptake (volume of distribution is approximately 66 L/kg) leading to a prolonged elimination half-life upward of 30–60 days with chronic oral therapy. This prolonged half-life limits the utility of electrophysiology studies until the drug has been eliminated. Side effects are relatively common (4–44%) and range from mild to severe reactions. These include slate blue skin discoloration, corneal deposits, hypothyroidism, and a potentially severe interstitial pneumonitis. Cardiovascular effects include bradycardia, heart block, QT prolongation with torsades de pointes, and hypotension. Side effects occur less frequently in children but mandate chronic amiodarone use only when potentially less toxic agents are ineffective. Limiting the dose and duration of amiodarone treatment can minimize side effects. In the pediatric critical care setting,

amiodarone is generally administered IV as a loading dose of 5 mg/kg, infused over 30 min or longer to avoid hypotension. Repeat doses are titrated to effect with a maintenance dose of 10–15 mg/kg daily. Amiodarone is commonly administered as a continuous infusion in the perioperative period when treating junctional ectopic tachycardia; a dosage range of 7 to 10 mcg/kg/min approximates standard daily mg dosing totals. Fluid for volume support and calcium chloride should be readily available if clinically significant hypotension ensues. Hypotension is more common with rapid IV administration; this can often be avoided using slower infusion rates or with oral administration.

18.5 Miscellaneous Antiarrhythmic Agents and Arrhythmias

18.5.1 Sotalol

Sotalol is a class III antiarrhythmic with class II properties useful for atrial tachyarrhythmias.

Sotalol is classified as a class III antiarrhythmic, as the primary mechanism of action is to block potassium channels. This results in a prolonged period of repolarization (and, subsequently, prolongation of the QTc interval). However, sotalol differs from other class III antiarrhythmics in that it also has beta-adrenergic blocking properties. This allows the drug to be used for the treatment of both atrial and ventricular dysrhythmias. The drug is most commonly used in children for the treatment of difficult-to-control atrial tachyarrhythmias and was first included in the 2010 American Heart Association's guidelines for the treatment of atrial fibrillation. While it was previously available as an oral medication, in 2015 it became available in the United States for intravenous use. Since that time, sotalol has been administered by both intermittent bolus dosing and continuous infusion. Limited pediatric experience reports that sotalol is safe and effective in the treatment of difficult-to-control atrial tachyarrhythmias such as atrial flutter and ectopic atrial tachycardias. Sotalol is renally excreted and should be used very carefully in patients with renal failure. Due to sotalol's ability to significantly increase the QTc, periodic ECG monitoring is mandated, and it carries a black box warning recommending patients only be started or stopped on this medication as an inpatient with monitoring of both cardiovascular status and creatinine clearance.

18.5.2 Magnesium for Torsades De Pointes/Long QT Syndrome

TdP is a specific polymorphic ventricular tachycardia seen in patients with prolonged QT intervals. It can be acute in onset and lead to syncope or sudden death.

Torsades de pointes (TdP) is a polymorphic ventricular tachycardia associated with a prolonged QT interval. This arrhythmia is encountered in individuals with the congenital long QT syndrome (LQTS) and in those with drug induced (or other secondary cause) for QT prolongation. Patients may suddenly develop TdP, often in response to an acute adrenergic stress. Precipitating stressors may include cold-water immersion (swimming), startling events, or strong emotions. Patients are often diagnosed with inherited LQTS during an evaluation of recurrent syncope or seizures, and this should be considered when evaluating patients after unexplained near drowning or syncope. The corrected QT interval calculated using Bazett's formula (QTc = QT/(square root of the preceding RR interval)) remains the standard screening tool for the LQTS. In general, the corrected QT interval should be less than 450 msec, with some normal females reaching as high as 460 msec. This is an inexact screening tool, as individuals with genetically proven and clinically significant LQTS have been doc-

umented to have QTc in the normal range. Syncopal events in patients with LQTS result from self-terminating bouts of torsades de pointes, any of which could ultimately degrade to ventricular fibrillation and result in sudden cardiac death. A number of inherited ion channel mutations have been identified as causative, with some individuals presenting with spontaneous mutations and a negative family history. An increasing number of gene mutations have been described, with growing knowledge as to their clinical significance. For example, specific potassium channel mutations (KvLQT1, *minK*, *HERG*, *MiRP1*) have been shown to interfere with potassium ion flow and prolong cell repolarization. Conversely, mutations in sodium channels (SCN5A) produce a "gain of function" that prolongs sodium flow and, with it, action potential duration.

Figure 18.9 shows an ECG from an adolescent female who presented with recurrent syncopal events. Her corrected QT interval was prolonged at 492 msec. This degree of QT prolongation is diagnostic but is not nearly as dramatic as is often seen in many families where the corrected QT interval can reach 550–600 msec or greater.

TdP first-line treatment is basic resuscitation principles with the addition of magnesium sulfate.

Torsades de pointes can be identified as a particular type of ventricular tachycardia with undulating, phasic changes in the QRS axis (Fig. 18.10). Basic resuscitation principles take precedence: the unstable patient with pulseless VT should be immediately defibrillated using 2 J/kg of energy. Epinephrine is recommended for the pulseless patient if defibrillation is unsuccessful. When TdP is identified, magnesium sulfate (25–50 mg/kg, maximum 2 g) should be administered. This has been shown experimentally to decrease triggered activity and, clinically, to effectively and safely suppress TdP in patients of all ages. Some data suggest that lower magnesium doses (5–10 mg/kg bolus followed by a continuous infusion of 0.5–1 mg/kg/h) may be effective to suppress bursts of TdP in children with inherited or acquired QT prolongation. Serum magnesium levels should be followed in children treated with magnesium sulfate to assure correction of hypomagnesemia and to limit the risk of side effects (somnolence, muscular weakness, respiratory suppression) that can be observed with high serum concentrations (>5 mg/dL).

18.5.3 Other Treatment/General Principles

Full cardiac evaluation is indicated for children with ventricular rhythm disorders. The cardiologist will attempt to assess the risk for recurrent arrhythmia and sudden death, balancing treatment recommendations accordingly. Similar

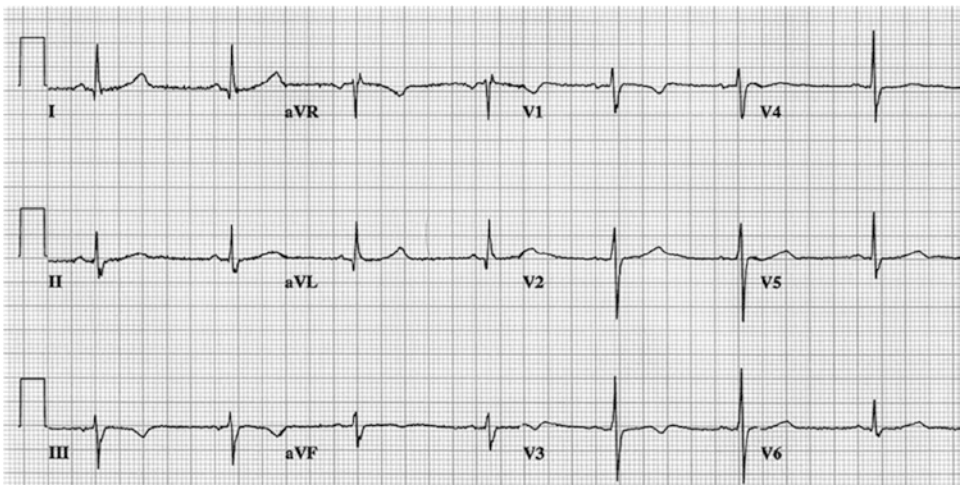


Fig. 18.9 12-lead ECG displaying long QT interval in an adolescent female with a history of recurrent syncope. Long QT syndrome is caused by cardiac ion channel mutations. Patients have a corrected QT interval >450 msec and are at risk for sudden death due to the onset of torsades de pointes and ventricular fibrillation. Episodes are typically precipitated by adrenergic stress and can present as recurrent seizures or syncope. Screening ECGs should be performed when caring for patients with unexplained syncope, seizures, or accidental events

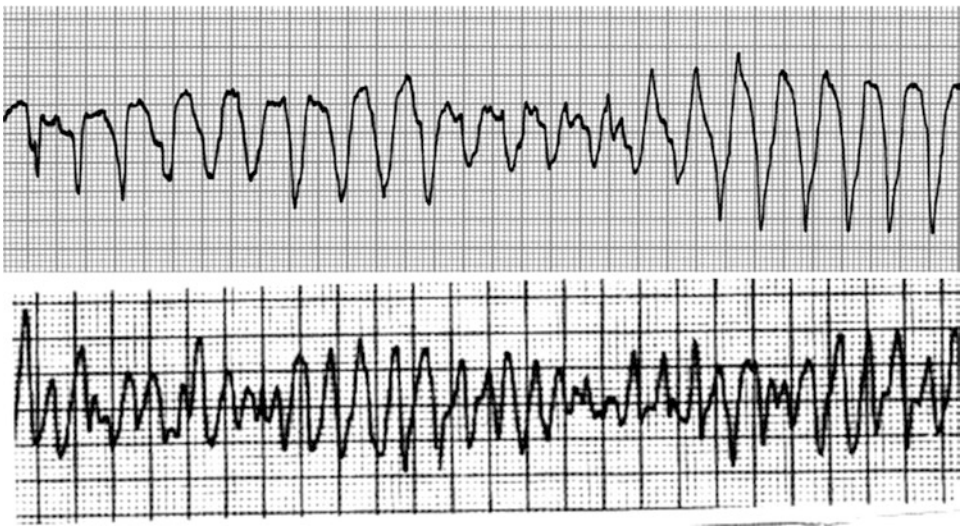


Fig. 18.10 Undulating pattern of a wide complex ventricular tachycardia characteristic of torsades de pointes

to the strategy used when treating supraventricular tachycardias, a wide variety of interventions are possible, titrated to risk and patient choice. Children with normal cardiac structure and function may not require any treatment for non-sustained periods of an accelerated idioventricular rhythm, which is a slow ventricular tachycardia typically at rates of 100–120 bpm. Patients with LQTS may be treated with ß-adrenergic blockade. Automatic implanted cardiac defibrillators (AICDs) are being increasingly placed in children with LQTS, hypertrophic cardiomyopathy, and similar disorders where defined risks of sudden cardiac death are possible. Catheter ablation is also effective for some conditions, such as RVOT ventricular tachycardia and some ectopic tachycardias.

18.6 Summary

A basic understanding of the normal cardiac conduction pathways is important in order to understand and distinguish between the various types of rhythm disturbances seen in the critical care setting. An overview of the rapid identification of rhythm abnormalities along with a basic understanding of the available antiarrhythmic agents and their mechanism of actions has been covered. Utilization of membrane-stabilizing mechanisms, such as calcium or magnesium administration, may be lifesaving in an acute situation, but consultation with a cardiologist regarding the management of nonurgent rhythm disturbances is always advised.

Review Questions

1. Which of the following statements is true regarding the cardiac action potential?
   - A. During hyperkalemia, calcium administration may be harmful by augmenting the calcium component of the resting potential.
   - B. The high potassium concentration within the cardiac myocyte contributes to the resting action potential.
   - C. The spreading wave of myocardial depolarization causes a negative deflection as it moves toward a surface ECG lead.
   - D. Sodium channel blockade with class IB agents (e.g., lidocaine) results in prolongation of the action potential duration.
   - E. Sympathetic augmentation decreases the inward calcium current and the slope of phase 4 depolarization.

2. Which one of the following mechanisms accounts for the most tachyarrhythmias (other than sinus tachycardia) in children?
   A. Ectopic foci.
   B. Nodal block.
   C. Reentry.
   D. Triggered activity.
   E. Vagal stimuli.

3. Which one of the following represents a class II antiarrhythmic medication?
   A. Amiodarone.
   B. Atenolol.
   C. Diltiazem.
   D. Lidocaine.
   E. Procainamide.

4. A 2-month-old female infant is being cared for in the pediatric intensive care unit for resolving viral bronchiolitis. You are called to the bedside to evaluate her for the sudden onset of a narrow complex tachycardia at a rate of 280 bpm. The infant is awake and interactive, although fussy and crying intermittently. Her blood pressure is 82/50 mmHg, her femoral pulses are readily palpable, and her capillary refill time is less than 2 s. Prior to the event, she had a documented normal sinus rhythm with no evidence of a delta wave. Which of the following interventions is *contraindicated*?
   A. Application of a bag of ice to the infant's face without establishing peripheral intravenous catheter.
   B. Placement of a peripheral intravenous catheter and administration of adenosine.
   C. Placement of a peripheral intravenous catheter and administration of digoxin.
   D. Placement of a peripheral intravenous catheter and administration of verapamil.
   E. Placement of a peripheral intravenous catheter and await input from a cardiology consult.

5. A 1-year-old male is admitted to the pediatric intensive care unit following closure of a large, unrestricted ventricular septal defect. The infant is receiving mechanical ventilation with his pulse oximeter consistently reading 98–100% breathing an inspired FiO_2 of 0.25. He is receiving heavy sedation to maintain synchrony with the ventilator. Several minutes following endotracheal suctioning, he suddenly became cyanotic and bradycardic. Evaluation of his cardiopulmonary monitor reveals a narrow complex junctional rhythm with a heart rate of 45 bpm and a blood pressure of 62/30 mmHg. The pulse oximeter is reading in the 50s and the patient is clearly cyanotic. Of the following choices, which is the most likely explanation for his bradycardia?
   A. Acute respiratory compromise with hypoxemia resulting in bradycardia.
   B. Atrioventricular dissociation from the surgical procedure.
   C. Sinus node dysfunction secondary to his surgical procedure.
   D. Sinus node suppression from required sedation.
   E. Vagally induced bradycardia from the suctioning.

6. Which of the following children is at **LEAST** risk for a sudden cardiac event?
   A. A 15-year-old, previously healthy female with scoliosis admitted following spinal fusion procedure having unifocal premature ventricular contractions.
   B. A 5-year-old male with preexcitation (Wolff-Parkinson-White syndrome) noted on his baseline electrocardiogram.

C. A 13-year-old female with syncope and a family history of long QT syndrome.
D. A 12-year-old male with a known cardiomyopathy having multifocal premature ventricular contractions.
E. An 8-year-old female with known long QT syndrome being started on methadone for chronic pain.

7. Which of the following medications used in the treatment of supraventricular tachycardia is contraindicated in the setting of Wolff-Parkinson-White syndrome due to the risk of accelerating anterograde conduction along the accessory pathway?
A. Adenosine.
B. Flecainide.
C. Digoxin.
D. Propranolol.
E. Sotalol.

Answers

1. B
2. C
3. B
4. D
5. A
6. A
7. C

Suggested Reading

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Postoperative Cardiac Care

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Contents

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Learning Objectives

- Discuss the epidemiology of congenital heart diseases and the multidisciplinary approach to management.
- Describe the pathophysiologic aftereffects of cardiopulmonary bypass relevant to postoperative care and organ dysfunction.
- Describe the principles and use of hemodynamic monitoring tools in postoperative cardiac patients.
- Describe the principles of mechanical ventilation in the postoperative management of cardiac patients.
- Describe low cardiac output syndrome and discuss postoperative management principles.
- Describe the physiologic effects of pulmonary arterial hypertension and discuss postoperative management principles.
- Discuss the diagnosis and management of postoperative arrhythmias.
- Describe acute kidney injury and management options in postoperative cardiac patients.
- Describe important clinical elements of the immediate postoperative encounter.
- Discuss critical issues in postoperative management of congenital heart defects including:
  - Left-to-right shunting lesions.
    - Patent ductus arteriosus (PDA).
    - Atrial septal defect (ASD).
    - Ventricular septal defect (VSD).
    - Atrioventricular septal defect (AVSD).
  - Left-sided obstructive lesions.
    - Critical aortic stenosis (AS).
    - Coarctation of aorta (CoA).
    - Interrupted aortic arch (IAA).
  - Ductal-independent mixing lesions.
    - D-transposition of great arteries (D-TGA) and arterial switch operation.
    - Total anomalous pulmonary venous return (TAPVR).
    - Truncus arteriosus.
  - Lesions with ductal-dependent pulmonary blood flow.
    - Tetralogy of Fallot (TOF).
  - Single ventricle lesions.
    - Stage 1: Norwood procedure.
    - Stage 2: Bidirectional Glenn operation.
    - Stage 3: Fontan operation.
- Discuss management of postoperative heart transplant patients.
- Discuss the importance and principles of nutrition support in postoperative cardiac patients.
- Discuss the causes, diagnosis, and treatment of chylothorax in postoperative cardiac patients.
- Discuss the causes, diagnosis, and treatment of diaphragmatic paresis in postoperative cardiac patients.
- Discuss the causes, diagnosis, and treatment of vocal cord paresis and paralysis in postoperative cardiac patients.

19.1 Introduction

Successful management of the postoperative pediatric cardiac surgical patient requires a thorough understanding of the pre- and postoperative anatomy and physiology of the patient, the impact of the surgical intervention, and the potential postoperative complications for each patient. This chapter intends to provide a clear and concise review of the most common and the most critical issues in the immediate postoperative care of congenital heart disease patients in the pediatric intensive care unit. The following text is written from the perspective of the pediatric intensive care specialist, and not all aspects of all congenital heart diseases are reviewed. Detailed anatomical description and classification, initial clinical presentation, physical examination findings, various diagnostic modalities, and long-term outcomes of each congenital heart defect are beyond the scope of this chapter. Therefore, readers should refer to separate pediatric cardiology or pediatric cardiothoracic surgery resources for this information.

19.2 Epidemiology of Congenital Heart Disease

Epidemiology: With improved surgical and medical care, about 85% of children with CHD are expected to live into adulthood.

Congenital heart disease (CHD) affects a large, ever-growing population of infants, children, adolescents, and adults. It accounts for 0.8–1.2% of all birth defects with a prevalence of 5.8–7.8 per 1000 people. About 40,000 babies are born with CHD every year in the United States. The disease burden for CHD is substantial. Cardiac defects are associated with lifelong comorbidity and significantly increase health services use during infancy and childhood. The surgical management of CHD is a cornerstone of comprehensive therapy. Development of cardiopulmonary bypass (CPB) made possible definitive repair of more complex defects, especially those with an intracardiac component. Many subsequent modifications in CPB, anesthesia management, surgical interventions and techniques, and patient selection led to increasingly successful interventions. With improved surgical and medical care, about 85% of children with CHD are expected to live into adulthood. Achieving this outcome necessitates the commitment of a diverse team of clinicians who specialize in the care of patients with complex CHD including pediatric intensive care specialists, cardiovascular surgeons, cardiac anesthesiologists, cardiologists, critical care nurses, respiratory therapists, pharmacists, and nutritionists.

19.3 Cardiopulmonary Bypass

Cardiopulmonary Bypass: CPB is a distinctly non-physiological state characterized by non-pulsatile blood flow, hypothermia, ischemia/reperfusion injury, inflammation, alterations in coagulation status, hemodilution, acid-base alterations, microembolization and oxidative stress.

Cardiopulmonary bypass (CPB) is used to divert the blood from the heart in order to perform complex congenital heart surgeries in a bloodless surgical field (See ◘ Fig. 19.1). Cardioplegia is also required to keep the heart still during the surgical repair. Cardioplegia is achieved by solutions with a high potassium concentration that inhibits myocardial cell repolarization and stops myocardial contraction. Cardioplegia solution can be administered into the aortic root during aortic cross clamp (antegrade infusion), or it can be administered into the coronary sinus (retrograde infusion) depending on the heart defect and the surgical repair.

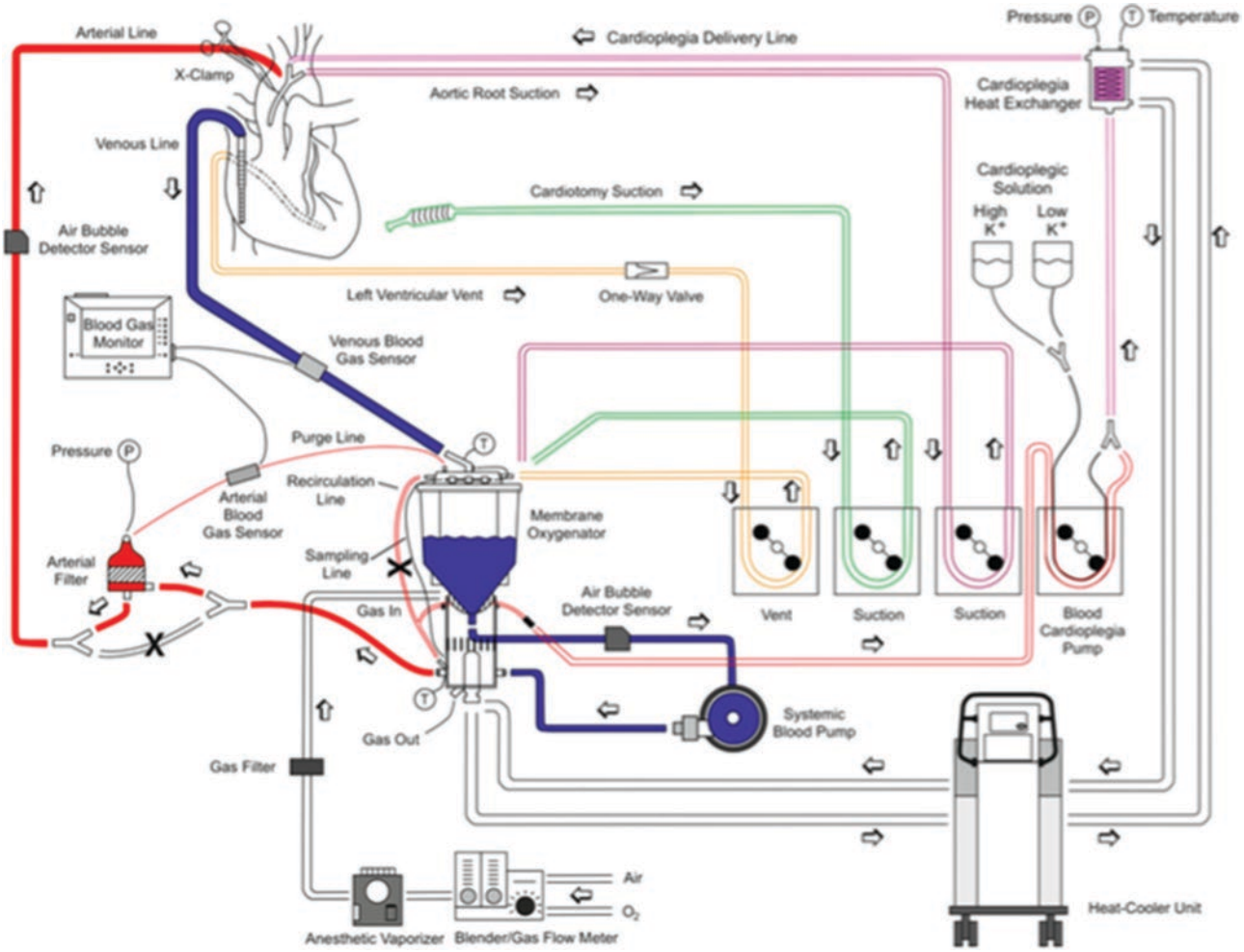


Fig. 19.1 Schematic diagram of typical cardiopulmonary bypass circuit. Illustrated are the systemic blood pump (*lower right*), oxygenator and venous reservoir (incorporated as a single hard-shell unit which also includes the heat-exchanger, depicted in the *lower center* of this diagram), cardiotomy suction (*upper center*), and arterial line filter/bubble trap (*lower left*). Also displayed are multiple safety devices and monitors, cardioplegia delivery, field suction and vent systems, gas and water delivery systems for the oxygenator and heat-exchangers. Not displayed is the central data processing and monitoring console

19.3.1 Cardiopulmonary Bypass-Induced Inflammation and Organ Dysfunction

Cardiopulmonary bypass–induced inflammation is triggered by multiple factors, including exposure of patient's blood to the artificial surface of the CPB circuit, ischemia/reperfusion, and hypothermia. Complex interactions between the complement system, coagulation system, fibrinolytic system, leukocytes, cytokines, platelets, and endothelium result from this exposure, eventually resulting in capillary leak and organ dysfunction. This CPB-induced postsurgical acute inflammatory response is the primary underlying pathophysiological process in the development of organ dysfunction by causing increased permeability of the blood-brain barrier, damage to the alveolar-endothelial barrier, decreased shortening of cardiac muscle cells, dysfunction of the systemic vascular endothelium, altered hypothalamic pituitary adrenal axis, injury to renal glomerular and tubular cells, and increased intestinal mucosal permeability.

Cytokines are the key molecules of acute inflammation following cardiac surgery. Individual cytokines may exert either proinflammatory or anti-inflammatory effects. Proinflammatory cytokine response to cardiac surgery includes tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), IL-6, and IL-8. Conversely, there is increased production of IL-10, a well-known anti-inflammatory cytokine. Cellular elements of the immune system also play a critical role in organ dysfunction in the setting of acute inflammation. Recent evidence highlights the importance of neutrophils in producing organ dysfunction in infants after CBP (Fig. 19.2).

Achieving immunological balance between pro- and anti-inflammatory responses is essential for healthy recovery following cardiac surgery. The counter-regulatory system to balance the pro-inflammatory response is called the compensatory anti-inflammatory response syndrome (CARS). Immunoparalysis is another term to describe the immunological state where the anti-inflammatory response dominates the pro-inflammatory response. Immunoparalysis is also described as a specific pathophysiological subcategory of pediatric multiple organ dysfunction syndrome that may occur in pediatric patients after CPB exposure. Laboratory findings of immunoparalysis following CBP include reduced levels of human leukocyte antigen-D–related (HLA-DR) expression (< 30%) on monocytes, reduced TNF-α production capacity (<200 pg/mL) in response to ex vivo stimulation with lipopolysaccharide, and increased levels of IL-10. Immunoparalysis following CBP in children is associated with a higher risk of postoperative infections and longer hospital stay.

Postoperative organ dysfunction is an important cause of mortality and morbidity in infants and children following cardiac surgery. As high as 81.8% of early postoperative mortality after cardiac surgery in children was attributed to multiple organ dysfunction. Infants and children undergoing cardiac surgery with CPB are particularly at high risk of developing postoperative organ dysfunction, specifically cardiac dysfunction/low cardiac output state requiring inotropic support, respiratory failure requiring prolonged mechanical ventilation, clinical/subclinical seizures, and acute kidney injury.

CPB-induced endothelial damage is responsible for capillary leak and generalized edema. The interaction between neutrophils and endothelium is a well-studied CPB-related mechanism of endothelial damage and organ dysfunction. As part of the inflammatory response, activated neutrophils bind to

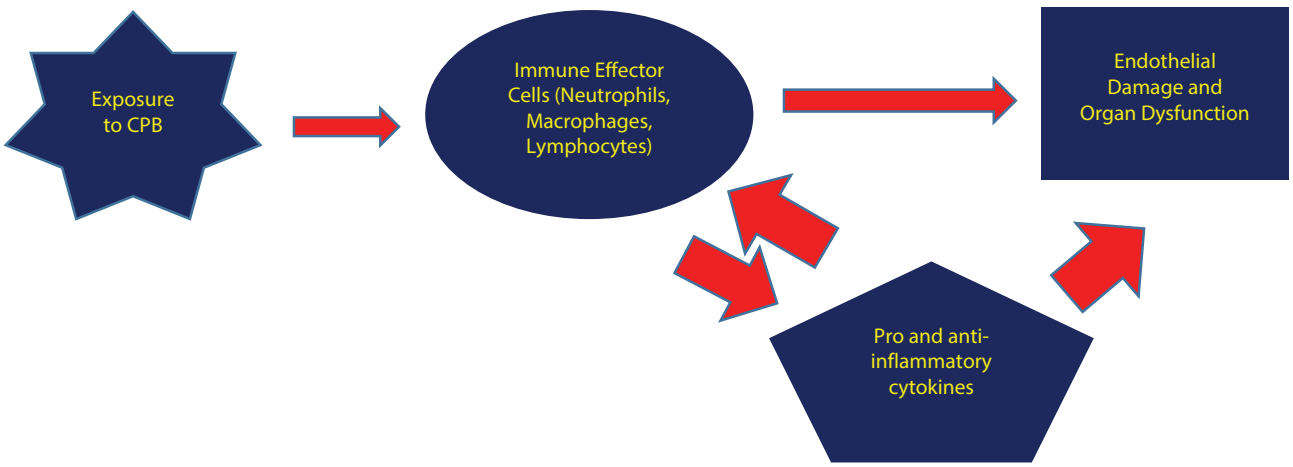


Fig. 19.2 Simplified schematic representation of the pathway to organ dysfunction induced by cardiopulmonary bypass (CPB)

endothelium via adhesion molecules such as selectins and integrins, eventually transmigrating out of the blood vessel and entering into the interstitial tissue of organs where inflammatory damage continues. Neutrophils also play an important role in lung inflammation, resulting in alveolar edema and inactivation of surfactant leading to increased alveolar-arterial oxygen gradient and decreased lung compliance. Reperfusion injury to the pulmonary vasculature and decreased nitric oxide production from injured endothelium are considered to be contributing factors to altered pulmonary vasculature reactivity and pulmonary hypertension that can be seen after CPB.

Effects of CPB on the myocardium are mainly due to ischemia-reperfusion injury. It is also suggested that inflammatory mediators may cause direct negative effects on the myocardium. Overall, CBP results in decreased cardiac contractility and myocardial edema causing decreased myocardial compliance. These myocardial changes significantly contribute to the postoperative low cardiac output state seen in some patients. The central nervous system, kidneys, and splanchnic circulation are also vulnerable to CBP-induced inflammation and ischemia-reperfusion injury. Furthermore, the CBP-induced inflammatory response causes increased intestinal permeability and bacterial translocation from intestines to the blood.

To attenuate the negative effects of CPB-induced inflammation and minimize organ dysfunction, systemic steroids have been studied extensively. Studies employed a wide variation in dosing and timing of steroids and reported conflicting results. However, preoperative steroid administration is still a common practice in many congenital heart disease centers. Heparin-coated CPB circuits decrease CPB-induced inflammation by decreasing complement and contact system activation. Removal of water by ultrafiltration during CPB is also thought to be effective in eliminating inflammatory cytokines and may improve postoperative cardiopulmonary function.

Cardiopulmonary Bypass-Induced Inflammation and Organ Dysfunction:

- Complex interactions between the complement system cascade, coagulation system, fibrinolytic system, leukocytes, cytokines, platelets and endothelium result from exposure to the CPB circuit, eventually resulting in capillary leak and organ dysfunction.
- Proinflammatory cytokines in the immune response to cardiac surgery include tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), IL-6 and IL-8. Conversely, IL-10 is the most well-known anti-inflammatory cytokine.
- Achieving immunological balance between the pro and anti-inflammatory response is essential for healthy recovery following cardiac surgery.

19.4 Perioperative Monitoring

Perioperative Monitoring:

Electrocardiogram (ECG), pulse oximetry, arterial blood pressure (invasive and/or non-invasive), and central venous pressure (CVP) are standard monitoring tools in postoperative cardiac patients. CVP monitoring is used to indirectly assess preload, but it is influenced by the compliance of the right ventricle. Depending on the heart defect and the surgical operation, left atrial pressure (LAP) monitoring is also used. LAP measurement is particularly useful in postoperative management of lesions with small left sided structures, (e.g., Shone's complex patients). For endotracheally intubated patients, end-tidal carbon dioxide ($ETCO_2$), peak inspiratory pressure, end-expiratory pressure, tidal volume, and other respiratory mechanics data should be monitored and recorded. Hourly urine output and strict fluid balance documentation provide essential data in the immediate postoperative period.

19.4.1 Near-Infrared Spectroscopy (NIRS) Monitoring

Near-Infrared Spectroscopy:
NIRS is a non-invasive technology that provides continuous venous weighted oxygen saturation of tissue beds of interest: renal, splanchnic, and brain.

Data on oxygenation status of the venous side of the systemic circulation provides valuable information to guide goal-directed interventions in shock states. NIRS provides continuous venous-weighted oxygen saturation of tissues. Unlike pulse oximetry, NIRS measures oxygen saturation of vascular beds with non-pulsatile blood flow. NIRS sensor uses light at two wavelengths (730 and 805 nm) emitted into the tissues, and two detectors in the NIRS sensor

measure the intensity of the reflected light. The change in the intensity of the reflected light at each wavelength is used to calculate oxyhemoglobin saturation of the tissue under the NIRS sensor. The depth of sampling beneath the NIRS sensor is about 2–3 cm, which is half of the source-detector distance in the NIRS sensor. While central venous oxygen saturation ($ScvO_2$) monitoring provides information about the global balance of oxygen supply and demand, NIRS allows clinicians to assess regional tissue oxygenation. Multi-site monitoring allows the assessment of regional tissue oxygenation, typically placing NIRS sensors on the forehead, flank, and abdominal wall.

NIRS is used in pediatric cardiac surgery patients most commonly to assess the adequacy of brain perfusion, and thus, to improve neurological outcomes in CHD surgery. Clinical studies demonstrated significant association of long-term neurodevelopmental outcomes with early postoperative cerebral oxygenation measured by NIRS. Experience in pediatric cardiac ICUs and recent publications support the use of NIRS measurement as part of goal-directed interventions in the perioperative management of congenital heart surgery patients. In a recent study by Hoffman et al., NIRS data predicted mortality and need for extracorporeal membrane oxygenation in the early postoperative period after stage 1 palliation of hypoplastic left heart syndrome patients.

19.5 Mechanical Ventilation

Mechanical ventilation is frequently necessary in the postoperative period after cardiac surgery. Positive pressure ventilation significantly impacts hemodynamics, especially in patients with myocardial dysfunction where it may reduce LV afterload and oxygen demand by reducing the work of breathing.

Pulmonary compliance decreases with increasing lung water content after CPB, which results from inflammation, reperfusion injury, and capillary leak. Decreased lung and chest wall compliance then lead to impaired pulmonary mechanics, which may manifest as increased work of breathing to the point of respiratory failure in neonates and infants with low baseline reserve. A considerable proportion of the total body oxygen (up to 20-25%) is consumed by respiratory muscles in severe respiratory distress, especially in the presence of concomitant LV dysfunction. Therefore, positive pressure ventilation to reduce the work of breathing can be beneficial. On the other hand, in children who undergo single ventricle palliation leading to passive pulmonary blood flow, for example, positive pressure ventilation may significantly impair pulmonary circulation; such patients benefit from early extubation.

As a general principle, increased mean intrathoracic pressure leads to a decrease in venous return and thus RV preload, although this effect may be temporized by augmenting intravascular volume immediately after the initiation of positive pressure ventilation. Pulmonary vascular resistance (PVR) and RV afterload are also affected by mechanical ventilation, as increased intra-airway pressure may overdistend alveoli, leading to increased resistance of intra-alveolar pulmonary vessels. However, low lung volumes and associated atelectasis may likewise increase resistance in extra-alveolar pulmonary vessels; in this instance using PEEP and positive pressure ventilation may reduce PVR and RV afterload.

Early extubation after cardiopulmonary bypass is increasing and is generally safe. Advantages of this approach include the reduction of the amount of postoperative sedation and length of stay in the ICU. Careful selection of patients for early extubation is necessary and should be discussed among car-

Mechanical Ventilation:
Pulmonary compliance decreases with increasing lung water content after CPB and may manifest as increased work of breathing to the point of respiratory failure in neonates and infants with low baseline reserve, especially in the presence of concomitant LV dysfunction. Therefore, positive pressure ventilation in this context can be beneficial. Conversely, in those infants or children who undergo single ventricle palliation leading to passive pulmonary blood flow, positive pressure ventilation may significantly impair pulmonary circulation; thus, such patients benefit from early extubation.

diac anesthesia, the cardiac surgeon, and the ICU team. Patients with high inotropic support, preoperative pulmonary hypertension, younger age, and long CPB times are at risk for extubation failure and need thorough evaluation before deciding upon extubation. If these patients fail extubation, both morbidity and ICU length of stay substantially increase. Protocolized assessment of patients for extubation readiness should also be considered in order to reduce the length of mechanical ventilation and decrease the risk of extubation failure. Diaphragmatic or vocal cord paresis/paralysis should specifically be considered in postoperative congenital heart disease patients who fail extubation (see Diaphragmatic Paresis and Vocal Cord Paresis or Paralysis sections of this chapter).

19.6 Low Cardiac Output Syndrome

Low cardiac output syndrome (LCOS), defined as a postoperative decline in cardiac output within the first 24 hours, was described in 1995 by Wernovsky et al. and occurs in up to 25% of neonates undergoing the arterial switch operation, with hemodynamic data indicating low cardiac index (<2.0 L/min per m^2) and high systemic and pulmonary vascular resistances. An oft-cited predisposing factor for LCOS includes the inflammatory effects of CPB (see CPB section and ◘ Fig. 19.2) on ventricular-vascular interactions, which may manifest as significant capillary-leak, systolic and/or diastolic dysfunction, and peripheral vasoplegia or vasoconstriction. Which vascular physiology predominates, however, likely depends on several factors, including patient age (post-CPB vasoplegia syndrome may develop in up to 25% of adult patients) and changes in lesion-specific perioperative pressure and volume loading conditions. As such, while still anticipating patient-specific perioperative risks (e.g., diastolic dysfunction in tetralogy of Fallot [TOF] or pulmonary hypertension status post repair of obstructed total anomalous pulmonary venous return [TAPVR]), a bedside-driven empiric approach using close hemodynamic monitoring and frequent reassessment remains the best way to ensure appropriate management for given changes in physiology. This should involve a systematic assessment of heart rate, rhythm, and stroke volume (preload, afterload, contractility) along with estimates of adequacy of tissue perfusion using NIRS and/or central venous oxygen saturation monitoring.

Included in therapies to maximize oxygen delivery are a variety of vasoactive agents (see ▶ Chap. 20). Their use should be tailored to the child's physiology, while also recognizing their potentially deleterious effects on increasing oxygen demand. Catecholamine-sparing agents, including milrinone, vasopressin, or calcium infusions in neonates, may be preferred as first-line agents under states of high metabolic stress depending on the neonate's clinical manifestations. Changes in cardiopulmonary interactions induced by adjusting mean airway pressure, lung volumes, and gas exchange may also significantly affect loading conditions on the postoperative heart. Reducing oxygen consumption through adequate sedation, treating hyperthermia, and minimizing work of breathing may help restore the balance between oxygen delivery and consumption. The use of stress-dose steroids in severe LCOS, while common (94% use based on a recent survey), continues to lack a strong evidence base, and is in need of further studies. Lastly, early use of extracorporeal life support should be considered in patients not responding favorably to medical management, and multidisciplinary discussions regarding candidacy and cannulation strategy should occur upon PICU admission.

LCOS: A systematic approach to LCOS management includes assessing heart rate, rhythm, and components of stroke volume (i.e., preload, afterload, contractility) to help ensure that appropriate therapies are utilized.

19.7 Pulmonary Arterial Hypertension

Pulmonary vascular pathology seen in patients with congenital heart disease includes both pulmonary arterial hypertension (PAH) (defined by mean pulmonary arterial pressure mPAP ≥25 mm Hg, pulmonary artery wedge pressure (PAWP) < 15 mm Hg, and pulmonary vascular resistance index (PVRI) > 3 Wood units/m^2) and pulmonary venous hypertension. While both can be associated with increased perioperative pulmonary vasoreactivity and over time precipitate fixed pulmonary arterial disease, management strategies sometimes vary markedly between the two pathologies. Perioperative management of PAH will be focused upon here.

Predisposing factors for PAH exacerbations include the already normally increased neonatal pulmonary vasculature tone, genetic predisposition (e.g., trisomy 21), lesions associated with increased pulmonary blood flow or high sustained pulmonary venous pressures (see ▶ Box 19.1), and the effects of cardiopulmonary bypass (CPB). While the exact mechanism of CPB-induced pulmonary vascular reactivity is still not well understood, it may be related to effects on the endothelium, which inhibit nitric oxide production, and the endogenous dysregulation of other vasoactive substances.

Pulmonary Hypertension:

- Hypoxemia with initial maintenance of hemodynamics often occurs during a PHTN exacerbation with an intracardiac shunt, whereas a low output state +/– significant oxygen desaturation often first presents in the absence of an intracardiac shunt.
- Management of PHTN crisis includes two global and interrelated strategies: (1) decreasing pulmonary vascular resistance (e.g., increased FiO_2, respiratory or metabolic alkalosis and/or using a pulmonary vasodilator) and (2) supporting right ventricular function.

Box 19.1 Congenital Heart Disease Categories Associated with Increased Risk of Pulmonary Vascular Disease

(a) Large left-to-right shunts.
- Large VSDs, AVSD, aortopulmonary window.

(b) Pulmonary venous hypertension/obstructive lesions.
- Cardiomyopathies, pulmonary vein stenosis, TAPVR, LV outflow tract obstruction, Shone's complex, isolated mitral valve obstructive disease.

(c) Cyanotic heart disease with increased pulmonary blood flow.
- Transposition of the great arteries (especially with VSD), truncus arteriosus, pulmonary atresia with VSD, univentricular heart (high pulmonary blood flow with or without a restrictive atrial septum).

VSD ventricular septal defect, *AVSD*: atrioventricular septal defect, *TAPVR* total anomalous pulmonary venous return, *LV* left ventricle

19.7.1 Pathophysiology of PAH

Clinical manifestations of pulmonary hypertensive crises result from two interrelated factors: (1) acute increase of the pulmonary vascular resistance and (2) the effect of the increased vascular resistance on ventricular performance and cardiac output. Triggers of increased pulmonary vascular resistance include: hypoxemia, acidemia, hyperthermia, and sympathetic stimulation related to pain/agitation. Hypoxemia in patients without intracardiac shunts, while not occurring in all patients, can be related to small airway obstruction from distended pulmonary arteries and perivascular edema, and may in severe cases lead to significant increases in airflow resistance and decline in lung compliance. Regarding acidemia, there is some evidence to suggest systemic pH may play a bigger role in affecting vascular resistance than pCO2 in the absence of acidemia, although both acidemia and hypercarbia should be avoided. Of note, excessively inflated or under-inflated lungs may exacerbate PVR through effects on the intra- and extra-alveolar vasculature, respectively.

Increased right ventricle (RV) afterload may lead to clinical signs of LCOS secondary to RV ischemia and failure, which reduces preload to the LV and thus low systemic blood flow. Furthermore, increased RV end-diastolic volume and

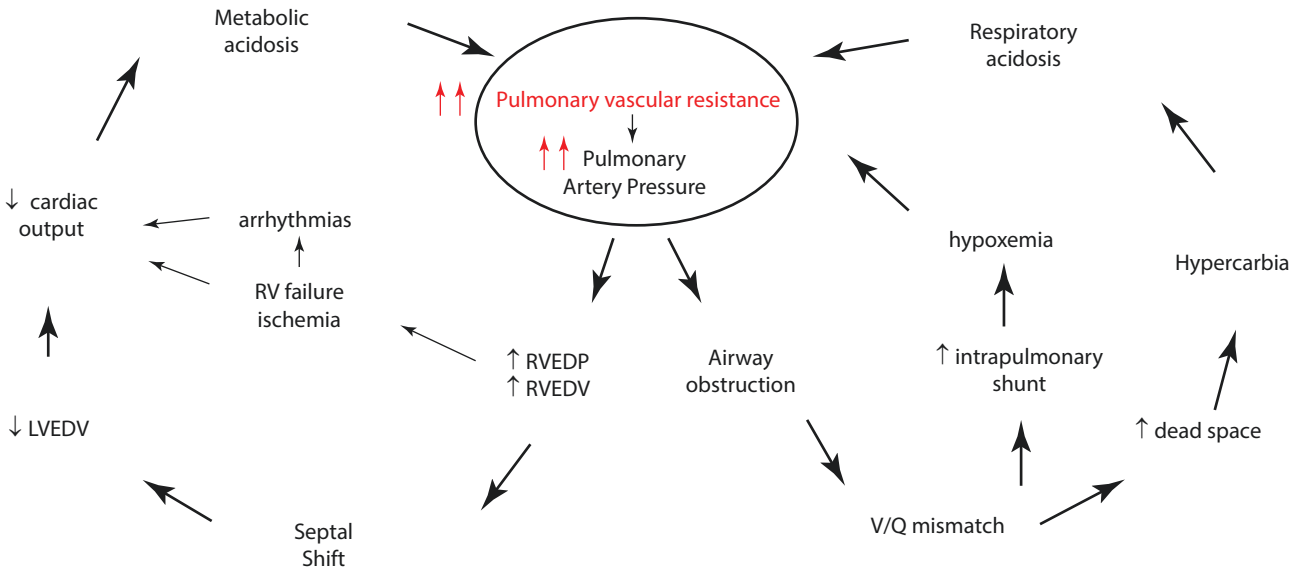


Fig. 19.3 Pathophysiology of PAH. LVEDV: left ventricular end-diastolic volume, RV: right ventricle, RVEDP: right ventricular end-diastolic pressure, RVEDV: right ventricular end-diastolic volume, V/Q: ventilation/perfusion ratio. (Reprinted from Shah and Szmuszkovicz 2017)

pressure shifts the interventricular septum toward the left ventricle (LV), leading functionally to LV diastolic dysfunction and compromised filling, which further reduces systemic output. Low systemic blood flow and pressure combined with increased RV end-diastolic pressure reduces RV coronary perfusion pressure (RV CPP = diastolic aortic root pressure – right ventricle end-diastolic pressure), which leads to RV ischemia and worse function, leading to a rapid downward spiral. This low output state also worsens acidemia that further increases PVR and decreases CPP, leading to a downward spiral (see Fig. 19.3).

19.7.2 Diagnosis

In addition to clinical recognition of LCOS, PAH exacerbation is characterized by high right-sided ventricular diastolic filling pressures documented by increased central venous pressure (CVP), and evidence of elevated right ventricular systolic pressures (>50% systemic) along with interventricular septal flattening and RV dilation on echocardiogram. Continuous direct measurement of pulmonary artery pressure remains the gold standard and should be considered in selected perioperative high-risk patients. Knowledge of the presence of a preexisting shunting or mixing lesion is paramount to interpreting bedside data, as in those patients who may shunt right to left. With PAH in this setting, hypoxemia is a first and early sign with an associated decrease in end-tidal CO_2, and the patient may not have signs of an immediate low output state unless hypoxemia persists. Those without a shunting lesion often present first with signs of a low output state, and although not common, may later develop hypoxemia through the mechanism described above.

19.7.3 Management of PAH

Two interrelated factors must be targeted for effective management of exacerbations: (1) decreasing pulmonary vascular resistance and (2) ensuring adequate RV function. Effective early interventions to decrease pulmonary

vascular resistance include increasing FIO_2 to 1.0, reversing acidemia through increasing minute ventilation and/or administration of sodium bicarbonate or tris-hydroxymethyl aminomethane (THAM), and sedation/muscle relaxation. Safely intubating such patients poses one of the biggest challenges in pediatric critical care and while doing so may allow for optimization of gas exchange and lung volumes; all precautions must be carefully considered including ECMO candidacy and standby. Inhaled nitric oxide (iNO), a fast-acting selective pulmonary vasodilator acting through a cGMP-dependent pathway, is considered first-line pharmacotherapy in perioperative exacerbations, and has the advantage of having minimal direct effect on the systemic vasculature. Often initiated at 20 PPM during a pulmonary hypertensive crisis, weaning iNO is often subsequently performed in a stepwise fashion given the association of rebound PAH with abrupt discontinuation. Nitrogen dioxide and methemoglobin levels should be monitored to avoid potential toxicities.

Sildenafil, a phosphodiesterase type 5 inhibitor, is sometimes used to facilitate weaning of iNO and is also used independently as primary therapy for PAH, although it has been associated with reduced systemic blood pressure and increased intrapulmonary shunting, especially when administered intravenously. Milrinone, also in the phosphodiesterase inhibitor family, acts as a nonspecific systemic and pulmonary vasodilator in addition to having modest inotropic properties and may be helpful during PAH exacerbations while keeping in mind the risk of systemic hypotension. Prostacyclin analogs, another class of agents used during exacerbations, are often used in cases refractory to the above agents and exist in both inhaled (inhaled iloprost and epoprostenol) and systemically administered forms. In choosing management strategies, anatomic causes of pulmonary venous obstruction and patients with left atrial hypertension should be investigated, as pulmonary vasodilation in these patients may exacerbate pulmonary edema by facilitating increased pulmonary blood flow and/or increased pulmonary capillary hydrostatic pressure.

RV failure may persist despite attempts to reduce RV afterload, and vasoactive agents should be strongly considered to support the RV, including inotropic agents to aid RV contractility and systemic vasoconstrictors to augment RV coronary perfusion pressure in the presence of preserved LV systolic function. For the latter, vasopressin is a promising therapy, given its unique action as both a systemic vasoconstrictor and pulmonary vasodilator. Management of RV preload can be difficult and should be based on close observation and reassessment as RV overdistension from fluid boluses can exacerbate RV failure.

19.8 Postoperative Arrhythmias

Preservation of an appropriate heart rate and AV synchrony is paramount to maintaining adequate cardiac output in the immediate postoperative period, as arrhythmias are common during this time. Several factors predispose cardiac surgical patients to develop arrhythmias, including myocardial dysfunction and edema following surgical resection, manipulation of cardiac tissue that may adversely affect the conduction system, electrolyte abnormalities, and finally the presence of a hyperadrenergic state resulting from both intrinsic and extrinsic catecholamine stimulation. Postoperative arrhythmias may cause significant hemodynamic instability and lead to a prolonged demand for mechanical ventilation, increasing need for inotropic support, and increased morbidity and ICU length of stay. Prompt and accurate diagnosis of arrhythmias is crucial for treatment; for example, ventricular tachycardia, which presents as a wide QRS complex tachycardia, can lead to rapid decline in cardiac output and should be quickly differentiated from SVT with aberrant conduction.

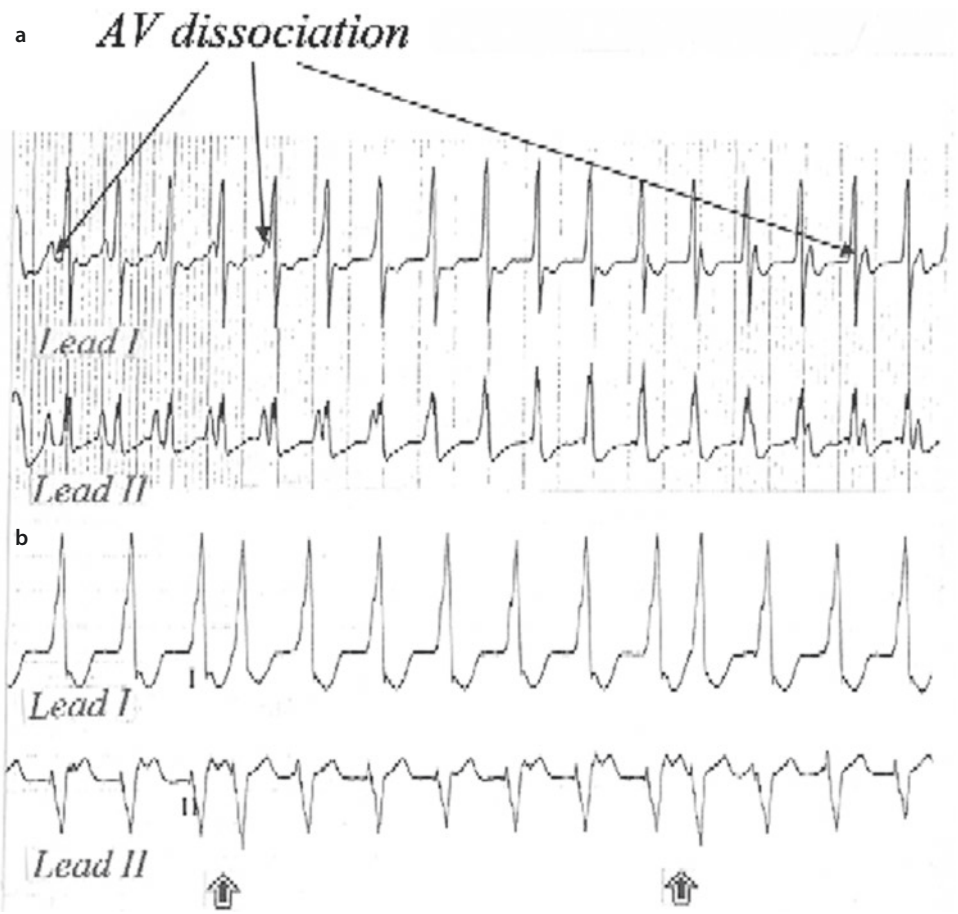
Most often, postoperative arrhythmias are attributed to one of the following mechanisms: enhanced automaticity (junctional ectopic tachycardia [JET], atrial ectopic tachycardia [AET]), reentrant excitation (reentrant SVT), conduction block (varying degrees of AV node block), or failure of impulse formation (bradycardia from sinus node dysfunction).

19.8.1 Sinus Tachycardia

Sinus tachycardia is a commonly encountered arrhythmia in the postoperative period as it is by triggered by fever, pain, agitation, anemia, hypovolemia, or a low cardiac output state. Heart rates that are extremely fast shorten diastolic filling time, which can compromise cardiac output, especially in patients with hypertrophied and non-compliant ventricles. Therefore, it is prudent to determine the underlying etiology to treat this rhythm.

19.8.2 Junctional Ectopic Tachycardia (JET)

JET results from enhanced automaticity within the atrioventricular node (AVN) or His bundle. JET most commonly occurs following VSD, AVSD, or tetralogy of Fallot repair. The rhythm is usually incessant, at a junction rate generally between 110 and 250 beats/min, and presents with AV dissociation or retrograde atrial conduction (◘ Fig. 19.4). A sudden change in heart rate with concurrent changes in the CVP tracing or blood pressure should alert caregiv-



◘ **Fig. 19.4** **a**, **b** Junctional ectopic tachycardia (JET). **a** Rhythm strip demonstrates JET with AV dissociation (*arrows* identify P waves), **b** rhythm strip of JET with intermittent short RR intervals (*double arrows*) due to sinus capture beats. (Reprinted by permission from: Springer, Critical Care of Children with Heart Disease Basic Medical and Surgical Concepts by Lee Beerman, Gaurav Arora, Sang C Par, 2009)

ers at the bedside. The diagnosis is made by examining the 12-lead ECG with a rhythm strip, and in some instances, the use of epicardial pacing wires to obtain an atrial electrogram is necessary to localize the P-waves and define the ventriculo-atrial relationships. Although it is a self-limited phenomenon, cardiac output can be significantly compromised in JET by reducing diastolic filling from the rapid heart rate and by the loss of coordinated atrial systole.

JET:
- Endogenous or exogenous catecholamines, fever and electrolyte disturbances usually exaggerate JET.
- Initial treatment is tailored toward minimizing both intrinsic and extrinsic catecholamines, repleting electrolytes, cooling to 35–36 degrees and atrial pacing at a rate slightly faster than the JET rate to restore AV synchrony and augment cardiac output.

JET is frequently unresponsive to pharmacologic therapy and is usually exacerbated by catecholamines and electrolyte disturbances. Therefore, initial treatment should be tailored toward minimizing both intrinsic and extrinsic catecholamines; this is achieved with aggressively treating fever and pain/agitation, reducing adrenergic drugs, and sometimes deepening sedation and neuromuscular blockade. In addition, repleting electrolytes and cooling to 35–36° centigrade should be implemented. Dexmedetomidine, an α_2-adrenoreceptor agonist, has been successfully used in cardiac intensive care units to treat JET, partly because of its sedative and analgesic effects and direct suppression of central nervous system–mediated adrenergic stimulation. In addition, dexmedetomidine can reduce the JET rate and may facilitate overdrive atrial pacing using a rate slightly faster than the JET rate to restore AV synchrony and augment cardiac output. Other therapies include the administration of either amiodarone or procainamide, both of which have been used successfully to treat JET. Both drugs have negative inotropic effects, so smaller doses and more prolonged administration times may help reduce the risk of sudden hemodynamic compromise.

19.8.3 Atrial Ectopic Tachycardia (AET)

This rhythm is a result of enhanced automaticity within an ectopic focus in the atrium. It presents as a narrow complex tachycardia, with P-wave morphology that is distinct from sinus P-waves and with a different P-wave axis on EKG. The tachycardia pattern typically presents with a gradual warming phase of increasing heart rate and a slow cooling down phase. Persistent AET may lead to arrhythmia-induced cardiomyopathy; therefore, treatment is necessary and should initially focus on correcting electrolyte abnormalities. Specific therapies should follow recommendations from an electrophysiology consultant and usually includes either procainamide or amiodarone. Digoxin may be used transiently to slow ventricular rate if hemodynamics are compromised because of the rapid ventricular rate. Cardioversion and atrial overdrive pacing may only transiently suppress this arrhythmia because the majority of the time this is not a reentrant tachycardia. Cardiac catheterization with ablation is usually used if the arrhythmia is unresponsive to maximal medical therapy.

19.8.4 Reentrant Supraventricular Tachycardia (SVT)

The term "SVT" is an imprecise term and often refers to an atrioventricular reentry tachycardia (AVRT) or AV nodal reentry tachycardia (AVNRT). These two are the primary substrates of reentrant SVT, manifesting as a reciprocating tachycardia with distinct antegrade and retrograde limbs in the reentry circuit. The main features of this arrhythmia are the sudden onset and termination, fixed cycle length, narrow QRS complexes, and either the absence of clear P-waves or the presence of retrograde P-waves. Management of this arrhythmia includes the termination of SVT and prevention of its recurrence. For termination of the tachycardia, vagal maneuvers, intravenous adenosine,

esmolol, or amiodarone can be considered. In the context of unstable hemodynamics, however, synchronized cardioversion should be used. Following the resolution of the SVT, an EKG should be performed to identify if the rhythm is now sinus and to assess if ventricular preexcitation is present, which indicates the presence of an accessory pathway as in WPW syndrome. The second part of management is the prevention of recurrence (e.g., correcting electrolyte abnormalities). If SVT is recurrent, consultation with an electrophysiology specialist and initiation of medical therapy such as beta-blockers or digoxin could be warranted.

19.8.5 Bradyarrhythmias

Bradyarrhythmias in the postoperative period include sinus bradycardia (e.g., sick sinus syndrome) and varying degrees of AV node block (Fig. 19.5). In the infant, cardiac output is heart rate dependent, especially in the postoperative period. Thus, bradyarrhythmias may be associated with low cardiac output states. Postoperatively, a complete atrioventricular block may occur after operations performed near the atrioventricular node as in VSD, AVSD and TOF repair. Bradyarrhythmias respond well to pacing using temporary pacing wires placed at the time of surgery. In isolated sick sinus syndrome, atrial pacing alone is adequate, while the AV node block often requires atrial sensing and ventricular pacing. Daily assessment of atrial and ventricular sensing and pacing thresholds is necessary; thresholds begin to rise with the development of

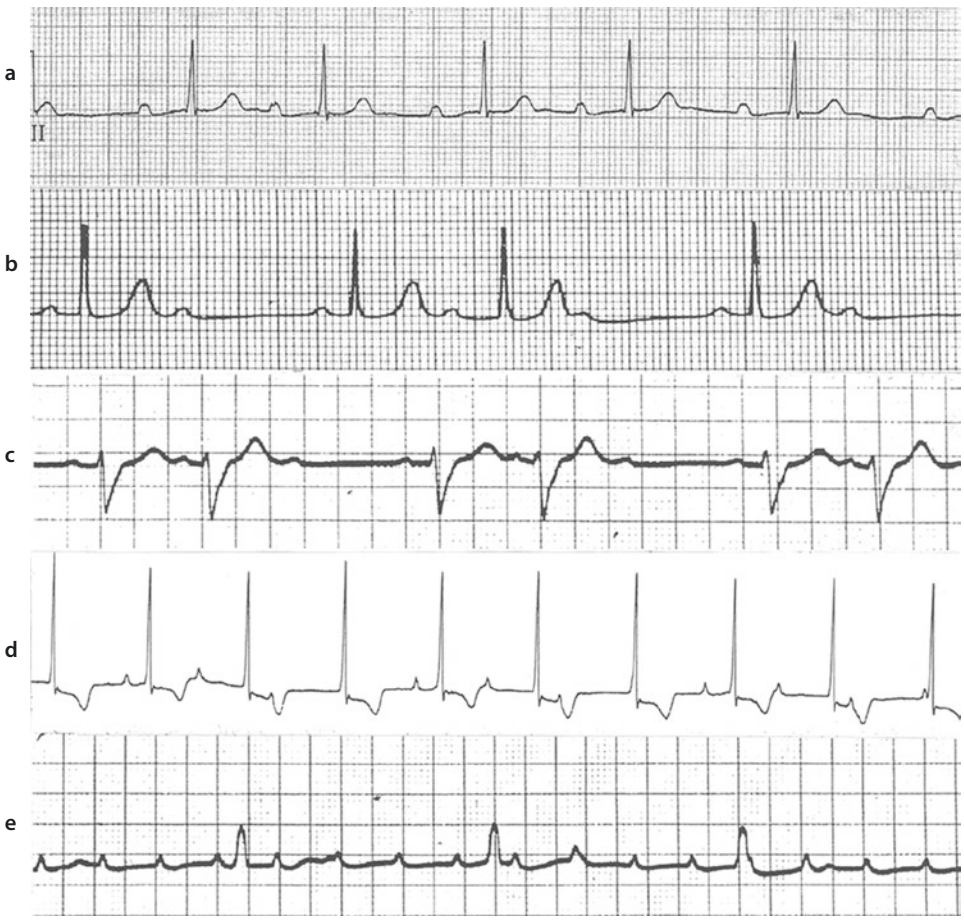


Fig. 19.5 **a**–**e** Types of AV block. **a** First-degree, PR interval is prolonged, but every P wave is conducted, **b** second-degree, Mobitz Type I (Wenckebach) block shows progressive prolongation of PR interval before a blocked P wave, **c** Second-degree, Mobitz Type II block shows no change in PR interval before the blocked P wave. Note wide QRS which is frequently associated with more distal AV block, **d** third-degree or complete AV block characterized by complete dissociation of atrial and ventricular activity. Narrow complex junctional escape rhythm suggests block is above the His bundle, **e** third-degree AV block with slow wide QRS escape rhythm indicates block is below His bundle and is an indication for urgent intervention. (Reprinted by permission from: Springer, Critical Care of Children with Heart Disease Basic Medical and Surgical Concepts by Lee Beerman, Gaurav Arora, Sang C Par, 2009)

fibrosis around the leads. Advanced second- or third-degree atrioventricular block that persists for at least seven days and that is not expected to resolve after cardiac surgery is considered a class I indication for pacemaker implantation.

19.9 Acute Kidney Injury Following Congenital Heart Surgery

Acute kidney injury (AKI) after congenital heart surgery is a significant problem that is associated with worse clinical outcomes. Identification of patients at risk for AKI, preventative measures, and early diagnosis and treatment are essential components of successful management of postoperative AKI. There are three diagnostic criteria used to identify acute kidney injury in children: (1) pediatric RIFLE (Risk, Injury, Failure, Loss, ESRD) developed by the Acute Dialysis Quality Initiative Group, (2) Acute Kidney Injury Network (AKIN) criteria, and (3) the Kidney Disease Improving Global Outcomes (KDIGO) classification system. Depending on the diagnostic criteria used, AKI has been reported in 30–60% of pediatric patients undergoing cardiac surgery. While serum creatinine has been the classical biomarker used in AKI diagnosis and monitoring, new biomarkers are being investigated to improve diagnostic sensitivity and prognostication. Among several other molecules, cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) seem to be the most promising new biomarkers of AKI.

In a study by Aydin et al., 458 pediatric patients (median age of 7.6 months) undergoing cardiac surgery were analyzed. Using RIFLE criteria, AKI was diagnosed in 51% of the entire cohort and in 60.9% of the patients younger than 1 month of age. Of those developing AKI, roughly 6% went on to require renal replacement therapy. Younger age, higher RACHS-1 (risk-adjusted classification for congenital heart surgery) category, and longer CPB time (>55 minutes for the cohort and >90 minutes for patients younger than 1 month of age) were identified as risk factors for developing postoperative AKI. Furthermore, AKI was found to be associated with longer duration of mechanical ventilation and length of PICU and hospital stay.

The pathophysiology of AKI following congenital heart surgery is not entirely understood, but literature supports that AKI is a multifactorial process in cardiac surgery patients. Alterations in renal perfusion, low cardiac output state, ischemic-reperfusion injury, oxidative injury, injury from nephrotoxic agents, hemolysis-induced free hemoglobin, and the inflammatory response induced by CPB are all thought to be contributing factors to AKI pathophysiology. Aminophylline, dexmedetomidine, fenoldopam, steroids, and intravenous acetaminophen have been investigated as potential agents to reduce the risk of AKI in cardiac surgery patients; however, there is no reliable evidence to support the use of those agents in the prevention of AKI following cardiac surgery in children.

Fluid overload in critically ill pediatric patients is associated with increased mortality and morbidity. Early postoperative fluid overload is also independently associated with worse outcomes in pediatric cardiac surgery patients. Therefore, prevention of fluid overload in postoperative cardiac surgery patients has become an important clinical goal. In a 2015 retrospective study by Kwiatkowski et al., early initiation of peritoneal dialysis (PD) in high-risk infants resulted in a higher percentage of negative fluid balance on postoperative days 1 and 2, shorter time to negative fluid balance, earlier extubation, improved inotrope scores, and fewer electrolyte imbalances requiring correc-

tion. A more recent study in 2017 prospectively comparing PD with diuretics in high-risk infants showed that PD was superior to diuretics in achieving negative fluid balance and shorter duration of mechanical ventilation.

PD is relatively easy to initiate and perform and is usually well tolerated (compared to hemodialysis) in hemodynamically unstable children. Similar to any foreign body, the PD catheter can be a source of infection (insertion site infection and peritonitis), and thus, protocols for its maintenance and timely removal should be routinely used.

Continuous renal replacement therapy (CRRT), unlike PD, allows for more rapid correction of serum electrolyte abnormalities and fluid overload. Commercially available circuits with small priming volumes, together with algorithms that allow maintenance of more exact fluid balance, have rendered CRRT feasible in infants after cardiac surgery. CRRT can be used in conjunction with ECMO. Such combined therapy can simultaneously address low cardiac output, severe respiratory failure, and symptomatic AKI, all of which may prove refractory to less-invasive treatments.

Acute Kidney Injury Following Congenital Heart Surgery:

- Younger age, higher RACHS-1 (risk-adjusted classification for congenital heart surgery) category, and longer CPB time are identified as risk factors for developing postoperative AKI.
- Early postoperative fluid overload is also independently associated with worse outcomes in pediatric cardiac surgery patients.

19.10 Immediate Postoperative Encounter

Postoperative care of the cardiac patient starts with the transfer of care from the operating room to the PICU personnel. The pediatric intensive care physician, bedside nurse, respiratory therapist and pediatric cardiologist who will be taking care of the patient should be present at the bedside during transfer of care to ensure that all team members receive consistent information from the operating room team and understand specific goals of care for the patient in the immediate postoperative period.

The cardiovascular surgeon should relate the details of the procedure performed, articulating the pre- and postoperative anatomy, echocardiography findings, and anticipated physiologic outcomes. This should include describing complications, if any, and identifying potential problems that require notification of the surgical team.

The cardiac anesthesiologist is expected to document and communicate the following important patient information as relevant for the case:

- Relevant non-cardiac problems and home medications.
- Baseline preoperative vital signs.
- Issues during the induction of anesthesia.
- Details of airway management.
- The number and location of venous and arterial catheters.
- Pre- and post-CPB inotropic support and trend of hemodynamic parameters.
- Dysrhythmias, presence of pacing wires.
- Duration of CPB, aortic cross-clamp, and circulatory arrest times; the degree of hypothermia achieved.
- The amount of intraoperative fluid and blood products administered.
- Intraoperative urine output amount and diuretics administered.
- Intraoperative ventilation/oxygenation issues, lung compliance, and current mechanical ventilator settings and last blood gas if available.
- Current sedative and analgesic medications as well as the timing of the last dose of neuromuscular blocker agent given.

Initial assessment of the postoperative patient should include heart rate, rhythm, arterial blood pressure, central venous pressure, arterial oxygen saturations, near-infrared spectroscopy (NIRS) values, level of sedation, ausculta-

tion of heart and lungs, quality of proximal and distal pulses, capillary refill time, and respiratory mechanics. Obtaining blood gas analysis (arterial and/or venous), lactate level, electrolyte concentrations including ionized calcium concentration, hemoglobin/hematocrit levels, platelet count, and coagulation tests should be considered in the immediate postoperative period. A chest radiograph should be obtained to evaluate the position of the endotracheal tube, vascular catheters, chest tubes, and lung fields to rule out the presence of pneumothorax, effusion, etc. An ECG should also be performed to document the cardiac rhythm in the immediate postoperative state.

19.11 Postoperative Management of Selected Congenital Heart Defects

All patients after cardiac surgery are at risk of a low cardiac output state, rhythm abnormalities, and post-surgical bleeding; and patients require adequate sedation and postoperative pain control. The following sections focus on selected lesion/surgery-specific pre- and postoperative issues relevant to the immediate postoperative intensive care unit management.

19.11.1 Left-to-Right Shunting Defects

Patent ductus arteriosus (PDA), atrial septal defect (ASD), ventricular septal defect (VSD), and atrioventricular septal defect (AVSD) are the typical heart defects causing left-to-right shunting of blood that results in increased pulmonary blood flow. If these heart defects are left untreated, they can cause pulmonary vascular obstructive disease. As the pulmonary vascular disease worsens over time, pulmonary vascular resistance increases and, if unchecked, may result in right-to-left shunting of blood flow, causing cyanosis that is called Eisenmenger syndrome.

19.11.1.1 Patent Ductus Arteriosus (PDA)

PDA results from a failure to close the vascular structure connecting the descending aorta to the pulmonary artery after birth. It classically results in left-to-right shunting from the aorta to the pulmonary artery, as the direction of blood flow depends on the relative resistances of pulmonary and systemic arterial vasculature. In premature infants, pharmacotherapy with ibuprofen or indomethacin can be attempted to induce PDA closure. If unsuccessful and clinically indicated, however, surgical ligation and division via thoracotomy may be performed. Postoperatively, such patients are at risk of recurrent laryngeal nerve injury and thoracic duct injury; therefore, these patients should be monitored for vocal cord paresis/paralysis and chylothorax in the postoperative period. Transcatheter closure techniques are an alternative to surgical closure in selected patients.

19.11.1.2 Atrial Septal Defect (ASD)

ASD is a defect in the interatrial septum. ASDs are classified into different categories: (1) primum ASD (associated with atrioventricular valvular abnormalities), (2) secundum ASD (most common type of ASD), (3) sinus venosus defect (associated with abnormal pulmonary vein connections), and (4) coro-

nary sinus defect (unroofing of the tissue separating the coronary sinus from left atrium). The magnitude and direction of the shunted blood flow at the atrial level depend both on the size of the defect and left and right atrial pressures, which reflect the relative diastolic compliances of the left and right ventricles. A systemic to pulmonary blood flow ratio greater than 1.5 is considered hemodynamically significant, leading over time to progressive volume loading of the right ventricle and may, if unaddressed, result in changes in the myocardium and pulmonary vasculature leading to pulmonary arterial hypertension in adulthood. Volume overload–induced right atrial enlargement may also result in atrial arrhythmias (e.g., atrial flutter or atrial fibrillation).

Hemodynamically significant ASDs require closure. Primum ASD, sinus venosus defects and coronary sinus defects are surgically closed. There are two options for closure of secundum ASDs: (1) percutaneously placed occluding devices and (2) surgical repair. Large secundum ASDs without adequate tissue margins to anchor occluding devices are considered poor candidates for device closure. Device embolization, pericardial tamponade, erosion through the atrial wall, atrial arrhythmias, and transient heart block are some of the postprocedural complications of this approach. Surgical closure is performed by either direct suture repair or patch closure. Short- and long-term outcomes of surgical closure are excellent. Almost all the patients are extubated in the operating room with minimal or no inotropic support. Postoperative patients should be monitored for dysrhythmias – specifically atrial arrhythmias – and pericardial effusion. Postpericardiotomy syndrome can complicate the postoperative course of any child undergoing open heart surgery. It presents with chest pain, fever, cough, fatigue, and emesis about a week or later after cardiac surgery; and it may, in rare cases, progress into cardiac tamponade that may require pericardiocentesis.

Atrial Septal Defect: Postpericardiotomy syndrome presents with chest pain, fever, cough, fatigue and emesis. It occurs about a week or later after cardiac surgery.

19.11.1.3 Ventricular Septal Defect (VSD)

VSD is a defect in the interventricular septum causing communication between the two ventricles. VSDs are one of the most common congenital heart defects (CHD) and can be found in isolation or as part of more complex CHDs. VSDs are classified as (1) muscular, (2) perimembranous, (3) subarterial, and (4) inlet-type defects. The amount of shunted blood through the VSD depends on the size of the defect and the relative resistances of the pulmonary and systemic vasculature. Left-to-right shunted blood flow through the VSD causes increased blood flow through the pulmonary vascular bed and results in increased pulmonary venous return, leading to increased volume load of the left heart. If the VSD is small and has an intrinsic flow limitation, then these are called restrictive VSDs.

VSDs are closed surgically using CPB. Access to the defect is usually achieved through either the atrioventricular or semilunar valves to avoid the need to perform a ventriculotomy. Selected VSDs can be closed by transcatheter methods, but it is not a routine practice due to high risk of heart block. Older patients without signs of heart failure preoperatively are typically extubated in the operating room. Others may benefit from staying intubated for the first postoperative night while hemodynamics stabilize. Patients may require inotropic support for a short period of time. Patients with longstanding excessive pulmonary blood flow in the preoperative period are at risk of postoperative pulmonary hypertensive crisis. Complete heart block is a known complication of VSD closure. If the complete heart block does not recover in 7–10 days following surgery, those patients require permanent pacemaker placement.

19.11.1.4 Atrioventricular Septal Defect (AVSD)

AVSD consists of atrioventricular valvar (AV valve) abnormalities along with interatrial and interventricular septum defects. AVSD is also referred to as atrioventricular canal defect. AVSD is especially known to be associated with trisomy 21. If the defect only involves the interatrial septum, then it is called a partial AVSD or primum ASD. When both interatrial and interventricular septums have defects, then it is known as a complete AVSD. Left-to-right shunt occurs via the atrial and ventricular septal defect(s) with high shunt flow likely from flow from the high-pressure LV to the atria through incompetence of the common AV valve. AVSD is treated surgically by patch repair of the atrial and ventricular septum and suture repair of AV valves. The surgical goal is to establish an intact atrial and ventricular septum and competent AV valves. Similar to other left–to-right shunting lesions, excessive pulmonary blood flow in the preoperative period puts patients at higher risk of pulmonary hypertensive crisis during the postoperative period. AVSD patients also have a higher risk of acquiring heart block following surgical repair.

19.11.2 Left-Sided Obstructive Lesions

This section focuses on critical aortic stenosis (AS), coarctation of the aorta (CoA), and interrupted aortic arch (IAA). Hypoplastic left heart syndrome (HLHS) is discussed separately in detail in another section of this chapter. Maintenance of systemic blood flow requires a PDA in these lesions. Therefore, these patients typically present with cardiogenic shock in the postnatal period as the PDA closes. Usually, these patients require prostaglandin E_1 infusion to keep the ductus open in the preoperative period.

19.11.2.1 Critical Aortic Stenosis (AS)

Congenital AS includes aortic annular hypoplasia and various forms of bicuspid or unicuspid aortic valves. If systemic blood flow depends on a PDA, this is usually referred to as critical AS, and these neonates/infants often present in shock at birth and often can have associated small left-sided structures. Critical AS can be addressed by transcatheter balloon valvuloplasty or surgical valvotomy; the latter is performed under CPB with aortic cross-clamping. Aortic valve regurgitation can be seen after transcatheter balloon valvuloplasty and surgical valvotomy. Neonatal Ross-Konno operation is performed in selected cases with a very small aortic annulus. In the setting of fixed postoperative residual aortic obstruction that limits the cardiac output, systemic afterload reduction is used cautiously due to a risk of decreased coronary artery perfusion pressure and flow postoperatively. The risk of postoperative pulmonary hypertension should be remembered if there is a history of preoperative left atrial hypertension.

19.11.2.2 Coarctation of Aorta (CoA)

There are a few different surgical techniques for CoA repair (i.e., end-to-end aortic anastomosis, patch augmentation, subclavian flap aortoplasty, and extended resection with primary anastomosis). If no other intracardiac lesions need to be surgically addressed and the transverse arch is of adequate size, CoA repair is typically performed through a lateral thoracotomy. During the repair, the PDA is also ligated and divided. Postoperative management is usually uncomplicated, but a lateral thoracotomy incision is considered more painful compared with sternotomy so that special attention to postoperative

pain management is indicated. Pre- and post-ductal invasive or non-invasive BP measurements, along with echocardiography, can be used to assess the degree of postoperative residual CoA. Recurrent laryngeal nerve injury, thoracic duct damage, and spinal cord ischemia due to aortic cross-clamping are potential complications and respectively may lead to postoperative vocal cord dysfunction, chylothorax, and neurological deficits in the lower extremities. Postoperative paradoxical hypertension is a known phenomenon after CoA repair and can be managed by nitroprusside and/or esmolol infusions. Postcoarctectomy syndrome is defined by systemic hypertension, abdominal distention/tenderness, feeding intolerance, and gastrointestinal bleeding, which requires bowel rest and aggressive management of systemic hypertension.

Coarctation of Aorta: Postcoarctectomy syndrome is defined by systemic hypertension, abdominal distention/tenderness, feeding intolerance and gastrointestinal bleeding, which requires bowel rest and aggressive management of systemic hypertension.

19.11.2.3 Interrupted Aortic Arch (IAA)

IAA repair is performed through a median sternotomy with VSD closure if present. IAA, especially type B, is associated with DiGeorge syndrome (22q11.2 deletion), and those patients should be monitored for hypocalcemia during the postoperative period. Similar to postoperative CoA repair, IAA repair patients have extensive suture lines in the aorta, which increases the risk of postoperative aortic bleeding if hypertension is not aggressively managed.

19.11.3 Ductal-Independent Mixing Lesions

19.11.3.1 Transposition of the Great Arteries and the Arterial Switch Operation (D-TGA, ASO)

Transposition of the great arteries with concordant atrioventricular and discordant ventriculoarterial connections (D-TGA) and no significant outflow tract obstruction is very commonly fully repaired with the arterial switch operation (ASO). Two keys to anticipating postoperative problems include (1) the recognition of possible LV deconditioning due to prolonged preoperative exposure of the LV to the lower resistance pulmonary circulation and (2) the risk of coronary ischemia resulting from intraoperative coronary artery manipulation and relocation via coronary buttons into the neoaorta.

Postoperatively these neonates generally do well and can be safely extubated within the first 12–24 hours, but they may present in the first 4–12 hours with LCOS, partly related to the effects of CPB and long perioperative ischemic times on the fragile neonatal heart. If LCOS occurs, the following must *always* be considered as well: (1) mechanical compromise of coronary blood flow and (2) "deconditioning" of the left ventricle. Mechanical compromise of coronary blood flow should be considered when LCOS does not respond to standard management. Any hemodynamically significant arrhythmia or ECG findings suggesting myocardial ischemia in a coronary distribution may exist as well. There should be a low threshold for repeat echocardiographic or cath imaging to assess for regional wall motion abnormalities and compromised coronary blood flow. Regarding the "deconditioning" of the LV following ASO, which is primarily observed in repairs done at an older age, the LV is exposed to the higher systemic vascular resistance and may need some time to adapt. Inotropic infusions and afterload reduction, such as low-dose epinephrine and milrinone, may be needed to support the ventricle in the immediate postoperative period. Hypertension should be avoided since it increases afterload on the potentially dysfunctional LV and puts stress on the fresh postoperative aortic suture lines, which increases the risk of bleeding.

19.11.3.2 Total Anomalous Pulmonary Venous Return (TAPVR)

In managing patients with TAPVR, the most critical postoperative management question is the presence and extent of preoperative obstruction of pulmonary venous flow. Patients with TAPVR and obstruction often enter the operating room with significant pulmonary venous hypertension, leading to acute pulmonary edema with poor lung compliance, along with significant concern of reactive pulmonary vasculature. Postoperative management can be challenging, and paroxysmal PAH crises should be anticipated and managed accordingly (see pulmonary hypertension section). The value of inhaled nitric oxide (iNO) has been clearly demonstrated in these patients. However, if persistent, or if clinical deterioration occurs during iNO initiation, the possibility of residual pulmonary venous obstruction should be actively investigated.

19.11.3.3 Truncus Arteriosus

Truncus arteriosus (TA), representing a single arterial trunk and semilunar valve from which pulmonary, systemic, and coronary circulations arise, is now very commonly repaired in the neonatal period. Although the neonatal myocardium adapts less well postoperatively to perioperative stressors, significant congestive heart failure and coronary malperfusion often arise from neonatal pulmonary circulation runoff and truncal valve insufficiency. Furthermore, if not corrected early, this lesion can result in irreversible pulmonary vascular disease. The surgery, essentially involving patch closure of the VSD and separation of the pulmonary circulation with placement of an RV-PA conduit, requires a right ventriculotomy and may necessitate truncal valve repair as well.

Postoperatively, other than LCOS from exposure of the neonatal myocardium to surgery, the following additional problems should be anticipated: pulmonary vasoreactivity, isolated RV dysfunction, and postoperative arrhythmias. Given often torrential pulmonary blood flow preoperatively in addition to the effects of CPB on the pulmonary vasculature, a high concern of pulmonary hypertension should exist, with close monitoring and early if not prophylactic initiation of iNO (see pulmonary hypertension section). Independent of this, the right ventricle in this lesion is often hypertrophied with evidence of diastolic dysfunction and, having undergone ventriculotomy, may exhibit signs of postoperative failure. Higher filling pressures may be needed to maintain adequate cardiac output. Lastly, postoperative arrhythmias associated with surgical repair to the interventricular septum may include junctional arrhythmias and heart block. Not infrequently, delayed sternal closure is employed in these patients to allow tissue edema to subside, given the above-stated concerns.

19.11.4 Lesions with Ductal-Dependent Pulmonary Blood Flow

19.11.4.1 Tetralogy of Fallot (TOF)

TOF is a complex disease with many variations (e.g., absent pulmonary valve, pulmonary atresia, major aortopulmonary collateral arteries). This section focuses upon the "classic" tetralogy of Fallot: A constellation of problems caused by anterior malalignment of the conal septum results in an unrestrictive anterior VSD with overriding aorta, multilevel obstruction to the right ventricular outflow tract (RVOT), and right ventricular hypertrophy. Although palliative shunts and RVOT stents are sometimes still performed as a bridge to full repair, almost all patients undergo full repair in early infancy and even

neonatally as the primary intervention, which includes VSD closure and various methods to relieve RVOT obstruction.

Postoperatively, these patients generally have an uncomplicated course, and early extubation (6–24 hours) is safe and effective in improving hemodynamics in patients with a favorable trajectory. However, when specific concerns of LCOS exist in the immediate postoperative phase, the following should be considered: (1) postoperative arrhythmias and (2) restrictive RV physiology. Postoperative irritation of the area surrounding the AV node can cause a range of arrhythmias from junctional ectopy to high-grade heart block; recent reports suggest a postoperative incidence of JET as high as 30%. Postoperative arrhythmias often resolve within the first 24–72 hours but can lead to significant hemodynamic compromise. See the arrhythmia section for more details on diagnosis and management. "Restrictive RV physiology," defined in prior studies as diastolic antegrade flow of blood across the pulmonary valve, which reflects a stiff RV with diastolic dysfunction in the context of usually preserved biventricular function, may be encountered in the immediate postoperative phase. This physiology may need higher right-sided filling pressures to maintain preload for adequate cardiac output, although side effects of sustained higher central venous pressures may include pleural effusions and ascites. Small fluid challenges, even in the context of a "normal" CVP, may be indicated with close assessment of response in indices or clinical signs of cardiac output. Milrinone may be of some benefit given its lusitropic effect. Positive pressure ventilation may impede venous return to an already preload sensitive right ventricle and increase the afterload against which it must pump; hence considering early extubation is very reasonable.

19.11.5 Single Ventricle Lesions

Atresia of an atrioventricular and/or semilunar valve results in single ventricle physiology, where complete mixing of systemic and pulmonary venous return typically occurs at the atrial and/or ventricular levels, leading to equal oxygen saturations in the pulmonary artery and the aorta. Ventricular output is divided between the competing pulmonary and systemic circulations; the amount of blood flowing to either the pulmonary circulation (Qp) or systemic circulation (Qs) is determined by the respective vascular resistances in these parallel circuits. A variety of congenital heart diseases fall into this physiology.

In general, these neonates are divided into two main categories: those with pulmonary blood flow obstruction with a single left ventricle (e.g., tricuspid atresia, double inlet left ventricle, pulmonary atresia with intact ventricular septum) and those with systemic blood flow obstruction with a single right ventricle (e.g., hypoplastic left heart syndrome (◘ Fig. 19.6) with variations of mitral valve and aortic valve atresia or severe stenosis). Other cardiac lesions with two ventricles may also present with single ventricle physiology (e.g., TOF with pulmonary atresia and truncus arteriosus). The cornerstone of preoperative management of these neonates involves balancing blood flow into the parallel circulations, providing adequate oxygen delivery without excessive volume load on the single ventricle, minimizing acidosis, and ensuring optimal end-organ perfusion.

Prostaglandin E_1 at a low dose (0.01 mcg/kg/min) is usually initiated immediately after birth to maintain ductal patency, and to avoid other dose-dependent side effects (i.e., apnea, fever, increased secretions, and capillary leak). Echocardiography is performed in the first few hours after birth to confirm the diagnosis.

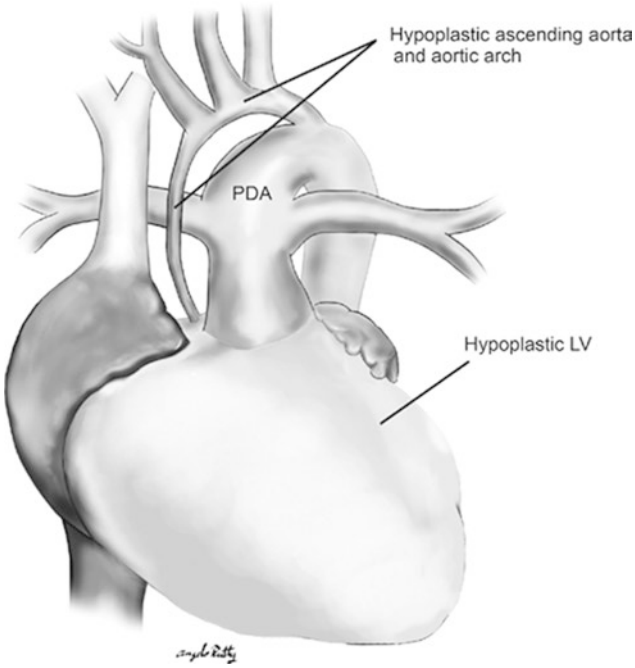


Fig. 19.6 Hypoplastic left heart syndrome. (Reprinted by permission from: Springer, Critical Care of Children with Heart Disease Basic Medical and Surgical Concepts by Yuliya A. Domnina, Ricardo Muñoz, Traci M. Kazmerski et al., 2009)

Based on the Fick principle: Qp:Qs = (SaO_2–SvO_2) / ($SpvO_2$–$SpaO_2$).

SaO_2: Arterial oxygen saturation, SvO_2: Venous oxygen saturation. $SpvO_2$: Pulmonary vein oxygen saturation, $SpaO_2$: Pulmonary artery oxygen saturation.

The ultimate goal is to have adequate systemic cardiac output with a Qp:Qs of ~1:1, manifesting as an arterial oxygen saturation of 75–80% and a systemic venous oxygen saturation of ~60%, assuming pulmonary venous saturation of 95%. This would result in mild ventricular volume load, and adequate systemic blood flow and systemic oxygen delivery. Do not rely on arterial oxygen saturation alone to estimate Qp:Qs as this could be deceptive. Indeed, an increasing oxygen saturation implies excessive pulmonary blood flow and potentially inadequate systemic flow.

Optimal clinical management relies upon understanding the role of pulmonary and systemic vascular resistance in determining systemic blood flow and in recognizing signs of inadequate systemic oxygen delivery. Clinical examination to assess peripheral perfusion, close monitoring of urine output, laboratory data including blood gas pH, lactate, mixed venous oxygen saturation levels, and other biomarkers of end-organ injury should be monitored closely. Measurements of regional venous-weighted oxygen saturations in both cerebral and somatic or renal regions using NIRS have become a standard of care in pediatric cardiac intensive care, as previously discussed.

A decrease in pulmonary vascular resistance occurs in almost all neonates after birth, and as this evolves over the first several days of life in an infant with single ventricle physiology, Qp:Qs increases, manifesting with higher arterial oxygen saturation, tachypnea, and respiratory distress. Often, the systemic output is still preserved, and if symptoms of congestive heart failure become apparent, cautious use of diuretics may be helpful.

If systemic perfusion becomes compromised, controlled mechanical ventilation, sedation, and paralysis may become necessary to improve the Qp:Qs ratio and minimize oxygen consumption. PVR may be increased by adopting a strategy to minimize the FiO_2, as necessary, to limit the vasodilatory effects of oxygen, permit a slight respiratory acidosis if on mechanical ventilation and/or supplement inspired carbon dioxide into the ventilator circuit. Maintaining a

hematocrit at ≥40% improves oxygen-carrying capacity and increases viscosity, which may increase PVR. In neonates with severe hypoxemia, ductal patency and the presence of an adequately sized atrial shunt should be confirmed; if an intact or restrictive atrial septum is present, transcatheter intervention with balloon or blade-mediated enlargement of the atrial septum should be considered.

The goal of staged surgical palliation for patients with single ventricle anatomy is to separate the systemic and pulmonary circuits, diverting systemic venous return directly to the pulmonary vascular bed, resulting in normal oxygen saturation and reducing the volume load on the single ventricle. This results in passive blood flow into the pulmonary vascular bed, which is improved with spontaneous breathing and may be impaired with positive pressure ventilation. The current sequence of single ventricle palliation in HLHS includes stage 1 reconstruction in the neonatal period, stage 2 bidirectional Glenn shunt between 4 and 6 months of age, and stage 3 modified Fontan between 2 and 3 years of age.

Single Ventricle Physiology:

Single ventricular output is divided between the pulmonary and systemic circulations. The common ventricle leads to equal oxygen saturations in the pulmonary artery and the aorta. The amount of blood flowing to either the pulmonary circulation (Qp) or systemic circulation (Qs) is determined by the resistance to flow into these parallel circuits.

19.11.5.1 Stage 1: Norwood Procedure

The goals of stage 1 palliation involve: (1) ensuring complete mixing of both pulmonary and systemic venous return at the atrial level, (2) securing unobstructed systemic blood flow from the right single ventricle, and (3) providing an adequate but controlled source of pulmonary blood flow. To achieve these goals, the classic Norwood procedure entails, respectively: (1) atrial septum resection, (2) aortic arch reconstruction (transection of the main PA, constructing a neoaorta using the main PA to augment the aortic arch and resected area of coarctation), and (3) insertion of modified Blalock-Taussig (mBT) shunt, which directs blood from the innominate artery to the pulmonary arteries via a polytetrafluoroethylene tube (◘ Fig. 19.7a), the size and length of which control the amount of pulmonary blood flow.

PVR is low compared to systemic vascular resistance; thus there is continuous forward flow into the mBT shunt throughout both systole and diastole. This results in lower systemic diastolic blood pressure and may lead to coronary hypoperfusion, which is referred to as "coronary steal." Hence, modification of the classic Norwood procedure, using a right ventricle → pulmonary artery conduit, was proposed by Sano and colleagues (◘ Fig. 19.7b). Advantages of RV-PA shunt modification include the elimination of diastolic runoff and "coronary steal," and fewer patients needing cardiopulmonary resuscitation during the Norwood hospitalization. These advantages must be weighed against the adverse effects from performing a ventriculotomy on the right (systemic) ventricle. In a large randomized controlled study (Single ventricle reconstruction trial) comparing the mBT shunt to the RV-PA conduit, there was a significantly higher risk of mortality in the mBT shunt group at the 12-month endpoint, but at longer follow-up this was no longer significant. In addition, in the RV-PA conduit group, stenosis at the distal anastomosis site was common and required multiple catheter interventions.

Postoperative management of patients after the Norwood procedure can be very challenging. Restoration of hemostasis early in the immediate postoperative period is essential, as bleeding is common given the substantial suture lines placed in the creation of the neoaorta. Attention is focused on balancing systemic and pulmonary blood flow and sustaining adequate perfusion to various organ systems. Measuring systemic venous oxygen saturation and/or NIRS (near infrared spectroscopy) is essential in the immediate postoperative period. Targeting a goal arterial oxygen saturation of 75–80% and maintaining arteriovenous oxygen saturation difference of 20–25% are important. Preferentially

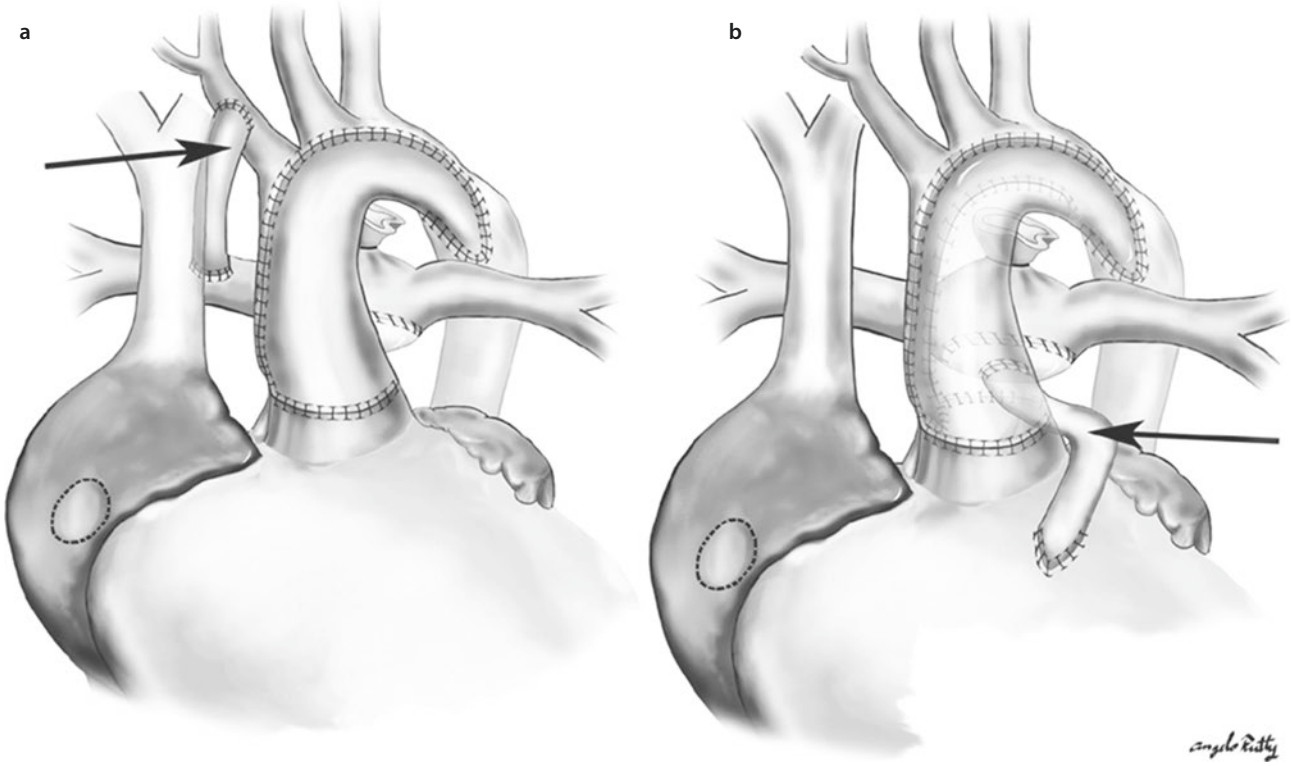


Fig. 19.7 **a** Right modified BT shunt; **b** Sano shunt. (Reprinted by permission from: Springer, Critical Care of Children with Heart Disease Basic Medical and Surgical Concepts by Yuliya A. Domnina, Ricardo Muñoz, Traci M. Kazmerski et al., 2009)

lowering systemic vascular resistance to divert blood flow from the lungs into the systemic circuit using systemic vasodilators can be effective. Conservation of systemic oxygen delivery is reliant on optimizing cardiac output and arterial oxygen content. Optimizing cardiac output requires attention to myocardial contractility, intravascular volume status (preload), systemic vascular resistance (afterload), heart rate, and rhythm. Therefore, inotropic agents, fluid boluses, vasodilators and/or vasoactive medications, and pacing could be necessary, especially in the immediate postoperative period. Arterial oxygen content depends on the hemoglobin concentration and arterial oxygen saturation. Therefore, maintaining adequate oxygen-carrying capacity is crucial. If shock develops, use strategies to minimize metabolic demand and allow for better matching of oxygen consumption to oxygen delivery. Sedative-analgesic medications and temperature regulation could be necessary to reduce metabolic demand. Use a ventilator management strategy that prevents atelectasis and avoids excessive work of breathing and hypocarbia; the latter lowers PVR and therefore can worsen systemic blood flow. Delayed sternal closure is a common strategy to reduce the risk of tamponade physiology in the immediate postoperative period. Outcomes after Norwood have improved significantly over the last two decades, likely due to broad improvements in perioperative care arising from a better understanding of single ventricle physiology and greater reliance on various monitoring devices.

19.11.5.2 Stage II Palliation: Bidirectional Glenn Shunt (BDG)

Bidirectional Glenn shunt procedure is the first step in separating the pulmonary and systemic circuits and entails conversion of pulmonary blood flow from a high pressure system (RV or aorta) to a low pressure venous source through anastomosis of the superior vena cava to the pulmonary arteries. The

Table 19.1 Causes of hypoxemia after superior cavopulmonary anastomosis

Pulmonary venous oxygen desaturation	Pleural effusion, chylothorax, pulmonary edema, atelectasis, pneumonia, or arteriovenous malformation
Systemic venous oxygen desaturation	Anemia, low cardiac output state, ventricular dysfunction, atrioventricular valve regurgitation, or veno-venous collateral
Decreased pulmonary blood flow	Increased pulmonary vascular resistance, pulmonary venous hypertension or obstruction of the pulmonary artery, or SVC-pulmonary artery anastomosis

preexisting mBT shunt or RV-PA conduit is removed during this stage. Advantages of BDG shunt include volume unloading of the single ventricle, thereby preserving its function and minimizing the risk of AV valve regurgitation, in addition to promoting more effective circulation by decreasing intercirculatory mixing while maintaining a Qp:Qs of typically 0.6–0.7.

The immediate postoperative management for the BDG emphasizes the maintenance of preload and early extubation to sustain normal cardiac output. If the patient remains intubated, then achieving normocapnia or mild hypercarbia may improve SVC → PA blood flow and improve oxygen saturation. Elevation of PVR after CPB may be minimized by using pulmonary vasodilators. In order to maintain adequate oxygen-carrying capacity anemia should be corrected in this admixture lesion.

Persistent hypoxemia after BDG could be due to any of the following (also see Table 19.1):

1. Systemic venous oxygen desaturation (anemia and/or low cardiac output, or the presence of a decompressing vein (i.e., veno-venous collateral from superior cavopulmonary circuit to the systemic ventricle)).
2. Pulmonary venous oxygen desaturations (e.g., from pleural effusions, atelectasis, pneumonia, pneumothorax, or pulmonary arteriovenous malformations).
3. Low pulmonary blood flow due to increased PVR, pulmonary venous hypertension or obstruction of the pulmonary artery, or SVC-pulmonary artery anastomosis.

Other common postoperative problems include pleural effusion, which is usually managed with diuretics and fluid restriction. High systemic venous pressures or perioperative lymphatic injury may precipitate chylous effusions as well (see chylothorax section). Systemic hypertension is also a very common phenomenon after stage 2, and may be related to pain and probably headache from the sudden rise in SVC pressure immediately following surgery. This is usually a transient phenomenon and often resolves in the first 24–72 hours after surgery. If SVC syndrome develops, further workup should be done to rule out thrombosis in the BDG shunt.

19.11.5.3 Stage 3: Fontan Operation

Francois Fontan was the first surgeon to separate the pulmonary and systemic circulation into a series circuit in the single ventricle patient. While the initial surgery was performed in a patient with tricuspid atresia, the concept is now applied to all patients with single ventricle anatomy.

The criteria for candidacy of Fontan completion include normal ventricular function, low pulmonary vascular resistance, absence of AV valve regurgitation, and the absence of pulmonary artery distortion. In this final palliative reconstructive surgery, blood flow from the IVC is routed to the pulmonary

artery using an extracardiac PTFE conduit of 18–22 mm diameter or through a lateral tunnel that is created within the right atrium. Some surgeons may create a small fenestration between the systemic venous pathway and the atrium, reducing pressure within the central venous system and pulmonary circuit and minimizing the risk of immediate postoperative low cardiac output, pleural effusions, and ascites at the expense of arterial desaturation and the risk of systemic embolization.

Postoperatively, patients ideally will have a Fontan pressure of 10–15 mmHg and a left atrial pressure of 5–8 mmHg with a transpulmonary gradient of 5–10 mmHg. Often, such patients are sensitive to changes in intravascular volume, given that the extrathoracic systemic venous pressure must be adequate to maintain blood flow across the pulmonary circuit. Treat hypovolemia if it occurs and maintain intravascular volume. Typically, these patients are extubated immediately after the procedure, as venous return to the heart and thus pulmonary blood flow occur mainly during inspiration in spontaneously breathing patients and positive pressure ventilation raises intrathoracic pressure and limits systemic venous return and pulmonary blood flow. If the patient returns from the OR intubated, extubation should be considered once hemodynamic stability with no active bleeding and adequate gas exchange have been achieved on modest support.

To differentiate the causes of low cardiac output after the Fontan procedure, using fontan pressure and LA pressure monitoring in conjunction can be helpful (see ◘ Table 19.2). If both pressures are low, this may be due to intravascular volume depletion. If the Fontan pressure is elevated and LA pressure is low, the differential diagnosis includes an increase in PVR, Fontan baffle obstruction, or pulmonary artery stenosis. Both elevated Fontan and LA pressures could be related to the following: ventricular dysfunction, AV valve regurgitation or stenosis, cardiac tamponade, or arrhythmias. Evaluation of persistent hypoxemia after Fontan completion with fenestration is similar to the prior discussion regarding BDG shunt; if a fenestration is present, the amount of blood shunting through the fenestration affects the arterial oxygen saturation.

Arrhythmias are not uncommon in the immediate postoperative period, and if associated with the loss of AV synchrony, these tend to be poorly tolerated. Prompt diagnosis and therapy are warranted. Other post-Fontan complications include pleural effusion, protein-losing enteropathy, hepatic fibrosis, and finally plastic bronchitis, which is rare but could be potentially fatal.

◘ **Table 19.2** Causes of low cardiac output state after Fontan operation

Fontan pressure low and LA pressure low	Fontan pressure high and LA pressure low	Fontan pressure high and LA pressure high
Hypovolemia	High pulmonary vascular resistance	Ventricular dysfunction
	Baffle obstruction or thrombosis	Atrioventricular valve stenosis or regurgitation
	Pulmonary artery stenosis	Arrhythmia, cardiac tamponade

LA left atrium

19.12 Postoperative Heart Transplantation Patient

Heart transplantation, now the standard of care in pediatric end-stage heart failure, requires both early recognition of potential candidacy and knowledge of perioperative complications by the pediatric cardiac intensivist. In the first 30 days postoperatively, primary graft failure, defined as compromised ventricular function requiring significant vasoactive and/or mechanical support in the absence of hyperacute rejection, remains the leading cause of mortality. Recipient preoperative risk factors that anticipate postoperative difficulties include liver/kidney dysfunction, ventilator dependence, diagnosis of congenital heart disease (vs. an acquired lesion), multiple reoperations, allosensitization, and pulmonary vascular disease. An indexed PVRi >6 Woods units/m^2 that is not responsive to vasodilator therapy is a common contraindication for transplantation; however, some newer data suggest no strong correlation between PVRi and postoperative mortality.

Postoperatively, in addition to standard medical approaches, early temporary use of mechanical circulatory support has been successful, although initiation of support in the context of a severe low cardiac output state has been associated with poor outcome. Special considerations should be made to support the right ventricle in the context of preoperative pulmonary vascular disease. Inhaled nitric oxide is commonly used in this circumstance, in addition to inodilators such as milrinone and low-dose epinephrine to support ventricular function. The loss of cardiac innervation should also be recognized as a unique postoperative issue, as normal stress-response induced chronotropy and inotropy can be blunted and inconsistent. Commonly used strategies to address this include the use of temporary pacing wires or pharmacological agents such as the nonspecific beta-adrenergic agonist isoproterenol. Any concerns about postoperative low cardiac output within the first 30 days should also lead to consideration of acute rejection as well as sepsis, given the high-dose immunosuppression administered in the immediate postoperative phase. Ultimately, a multidisciplinary approach to postoperative management is critical to ensure optimal outcomes.

19.13 Other Postoperative Issues

19.13.1 Nutrition

Infants with complex congenital heart disease are known to exhibit impaired weight gain during the first several months of life, and the ICU and postoperative course can significantly negatively impact growth. Within the ICU, lower caloric intake has been associated with longer need for mechanical ventilation and longer length of stay. Existing evidence suggests that 93% of postoperative children do not reach 90% of basic metabolic requirements by postoperative day 4, and that a 1 standard deviation weight-for-age Z-score decrease occurs in infants with single ventricle physiology between the time of shunt palliation and hospital discharge. Perioperative metabolic dysregulation and associated failure to recognize energy needs likely contribute to this, as most published predictive equations are inaccurate when compared to caloric requirements determined by indirect calorimetry (IC), which is difficult to perform. Moreover, other contributing factors include caloric restriction due to fluid restriction, frequent feed interruptions, inability to absorb nutrients, and large variations in practice regarding timing and mode of feeding initiation.

Controversies regarding the risk of perioperative enteral feeding while on vasoactive infusions, during umbilical artery catheter use, and with ductal-dependent lesions all remain, which reflects the lack of definitive data addressing such issues in this patient population. Strategies to optimize nutrition can include: using IC when possible to better estimate caloric needs, initiation of parenteral nutrition within the first week if tolerance of higher volumes of enteral nutrition during that time is not anticipated, using early gastric and transpyloric feeds in those at risk of dysphagia, early calorie concentration of feedings in fluid-restricted patients, and the use of feeding protocols to achieve consistency and minimize interruptions. The use of breastmilk in infants with a perceived risk of necrotizing enterocolitis (NEC) is reasonable, given its association with decreased NEC incidence in premature infants.

19.13.2 Chylothorax

The postoperative leakage of lymphatic fluid into the pleural space may result from surgical disruption of the thoracic duct or one of its main tributaries, and/or from increased pressure within the intrathoracic lymph system, e.g., secondary to central vein thrombosis or venous hypertension. Bidirectional Glenn (BDG) operation, Fontan-type procedure, TOF-repair associated with right ventricular diastolic dysfunction are all associated with a higher incidence of chylothorax due to central venous hypertension. Surgical operations in the vicinity of the thoracic duct, including systemic-to-pulmonary arterial shunt insertion, repair of aortic coarctation, and patent ductus arteriosus ligation may also predispose to the development of chylothorax. The development of chylothorax soon after the operation suggests traumatic laceration, while a later onset suggests central venous thrombosis or hypertension. The diagnosis of chylothorax cannot be based on appearance alone. It is established when the pleural fluid contains a triglyceride level of more than 1.24 mmol/L (110 mg/dL) or an absolute cell count >1000 cells/ mL with a lymphocyte fraction >80%. The most consistent diagnostic marker is the predominance of lymphocytes. Conservative treatment should begin with medium-chain triglyceride (MCT)-enriched diets, after ruling out venous thrombosis and/or hypertension. If the chylothorax persists, treatment with somatostatin, or the somatostatin analogue, octreotide, may be considered. Regular monitoring of liver function, blood glucose, and thyroid function tests is recommended during the administration of either somatostatin or octreotide; and necrotizing enterocolitis was reported in association with octreotide treatment. In children with chylothorax, intravenous albumin 25% and immunoglobulin supplementation may be necessary to maintain adequate serum albumin and immunoglobulin G levels. Antithrombin loss in chyle has been associated with the development of thrombosis after CPB operations. The role and impact of thoracic duct ligation in the management of persistent chylothorax are not clear. Other surgical procedures are described, including chemical pleurodesis and placement of a pleuroperitoneal shunt.

19.13.3 Diaphragmatic Paresis

Diaphragmatic paresis or paralysis may occur if injury to the phrenic nerve occurs. Neonates and small infants rely on a functioning diaphragm to maintain vital capacity; in this population the compliant chest wall combined with immature accessory and intercostal muscles lead to a reduced ability to compensate for a dysfunctional diaphragm. Transient palsy or permanent injury to the phrenic nerve, usually the left phrenic nerve, occurs during operations that

involve dissection of branch pulmonary arteries (TOF repair and Arterial switch operation) or during aortic arch reconstruction as in the Norwood operation or interrupted aortic arch repair.

Clinical suspicion is important to diagnose this condition. Clinical signs include increased work of breathing during ventilator weaning, hypercapnia, low lung volumes on the affected side, and an elevated hemidiaphragm on chest x-ray. Ultrasonography or fluoroscopy confirm the diagnosis with findings of diaphragm dysfunction and classical paradoxical motion. Recovery of the phrenic nerve may occur if it is a temporary paresis. Attempt to extubate after optimizing nutrition and cardiovascular status. If lung volume loss and failed extubation recur, then surgical plication of the diaphragm should be considered.

19.13.4 Vocal Cord Paresis or Paralysis

Post-extubation stridor presents as raspy and noisy breathing and is most likely due to mucosal swelling of the glottis or the trachea. If the stridor is persistent, or if the patient required reintubation, the clinician should rule out unilateral vocal cord paresis or paralysis, which is characterized by a weak, sometimes hoarse cry, weak cough and biphasic stridor. Direct laryngoscopy to evaluate vocal cord mobility is necessary to confirm the diagnosis, especially in patients with surgery near the recurrent laryngeal nerve (e.g., aortic arch reconstruction or aortic coarctation repair). Nerve function may return after a few days if the recurrent laryngeal nerve was traumatized but not transected.

19.14 Summary

The immediate postoperative management of congenital heart disease patients in the intensive care unit can be challenging and requires not only a thorough understanding of cardiovascular pathophysiology but also depends on a multidisciplinary team approach to provide the best care for these patients.

Review Questions

1. A 4-month-old infant is admitted to the PICU following complete repair of tetralogy of Fallot. Upon arrival, he is intubated and pharmacologically sedated. He is noted to have a regular, narrow complex, progressive tachycardia with a heart rate of 174 bpm and CVP of 15–20 mmHg. There are no discernible p-waves. He has adequate peripheral pulses and a blood pressure of 75/45 mm Hg. He is receiving a continuous infusion of milrinone (0.5 mcg/kg/min). The most appropriate initial treatment for this infant is which of the following?
   A. Administer a dose of adenosine (0.1 mg/kg).
   B. Administer a dose of furosemide (1 mg/kg).
   C. Avoid fever and stimulation, and assess and correct any electrolyte abnormalities.
   D. Decrease his sedation and allow him to become more awake.
   E. Initiate a low-dose epinephrine infusion (0.05 mcg/kg/min).

2. A 6-month-old female patient with Down syndrome is admitted postoperatively following successful two-patch repair of complete AV septal defect with no postoperative residual defects. Soon after arrival during endotracheal tube suctioning, she is noticed to have increased mottling with associated narrow complex tachycardia ranging around 180 bpm, arterial BP 60s/40s, and arterial oxygen saturations ~91%. CVP tracing appears to have normal morphol-

ogy, but was previously 8–10 mm Hg and is now trending in the low 20s with downward trending brain and splanchnic near-infrared spectroscopy (NIRS) readings. The next appropriate step should include:

A. Increase FiO_2 to 100% and hand ventilate.
B. Administer 2 mcg/kg fentanyl bolus.
C. 5 ml/kg 5% albumin bolus.
D. Amiodarone 5 mg/kg bolus.
E. Preparation for cardioversion.
F. A and B.

3. A 2-month-old male patient who is postoperative day 4 after the repair of aortic coarctation is in the PICU. The patient was extubated 3 days ago and oral feeding was started 2 days ago. His cry has been noted to be very weak and coarse in addition to mild biphasic stridor since extubation. The infant is also noted to be coughing frequently during oral feeding. An anterior-posterior view chest X-ray film was reported to be normal except for right upper lobe opacity. The arterial oxygen saturations are >95% in room air despite being mildly tachypneic. What would be the most appropriate next step in evaluation of this patient?
   A. Upper GI study.
   B. Perform bedside direct flexible laryngoscopy and speech therapy consult.
   C. Infectious diseases consult for initiation of systemic antibiotics.
   D. Obtain Computed tomography (CT) of chest.
   E. Ultrasonographic evaluation of diaphragm mobility.

4. A 7-day-old 2.6 kg neonate with hypoplastic left heart syndrome is admitted to the pediatric intensive care unit following stage I palliation (Norwood, 3.5 mm mBT shunt). The patient is receiving fentanyl (2 mcg/kg per hour), milrinone (0.5 mcg/kg per min) and epinephrine (0.08 mcg/kg per min). Initial ventilator settings include a tidal volume of 8 mL/kg, 28 breaths/min, PEEP of 5 cm H_2O, and FiO_2 of 0.4. The patient has delayed capillary refill time with cold extremities. The arterial blood pressure is 52/32 mm Hg (mean 38 mm Hg) and the atrial pressure is 14 mm Hg. An arterial blood gas sample shows a pH of 7.14, $PaCO_2$ of 38 mm Hg, PaO_2 of 70 mm Hg, HCO_3– of 15 mEq/L, SaO_2 of 93%, and lactate is 7 mmol/L with SVC oxygen saturation of 40%. Of the following, the BEST next step in the management of this patient is:
   A. Administer a fluid bolus of 5% albumin.
   B. Reduce the FiO_2 to 0.21.
   C. Decrease the epinephrine dose to 0.05 μg/kg per min.
   D. Administer an intravenous bolus of sodium bicarbonate.
   E. Increase the ventilator rate.

5. A 3-year-old child with tricuspid atresia who had a bidirectional Glenn shunt at 6 months of age now is admitted to the PICU after fenestrated lateral tunnel Fontan procedure. The patient is hypotensive with decreased urine output and delayed capillary refill. His vital signs are as follows: Heart rate 140 bpm with a sinus rhythm, BP 55/38, left atrial pressure is 5 mm Hg, venous pressure (Fontan pressure) is 6 mmHg and arterial saturations is 92%. Patient is receiving milrinone at 0.5 mcg/kg per minute and epinephrine at 0.05 mcg/kg per minute. What is the most likely diagnosis?
   A. Pulmonary hypertension.
   B. Ventricular dysfunction.
   C. Severe AV valve regurgitation.
   D. Hypovolemia.
   E. Fontan baffle obstruction.

Answers

1. C.
   Explanation: This scenario depicts a common postoperative problem following tetralogy of Fallot repair: Junctional ectopic tachycardia (JET). Commonly occurring in the first 1–3 days postoperatively, clues to the diagnosis include a narrow complex tachycardia driven by the junctional ectopic focus with AV dissociation or retrograde atrial conduction. Often, it is difficult to discern P waves on bedside telemetry; the use of epicardial atrial wires to perform an atrial electrocardiogram may be helpful to better discern the AV relationship. The CVP waveform tracing should be examined for the presence of "cannon" A waves resulting from atrial contraction against a closed tricuspid valve. Although one may expect higher CVP values in TOF given postoperative restrictive RV physiology, higher values should also lead to consideration of AV dissociation. Management of JET in the relatively stable patient first includes supportive measures, but may then include both pharmacotherapy and/or atrial overdrive pacing if incessant. Exogenous catecholamines such as epinephrine may stimulate and exacerbate this rhythm and should be minimized if possible.

2. F.
   Explanation: The above patient has several risk factors for postoperative reactive pulmonary vasculature, including Trisomy 21, young age, exposure to CPB, and having a defect (AV septal defect) commonly associated with this condition. Often with noxious stimuli such as endotracheal tube suctioning, this may manifest as evidence of LCOS with acute elevation in CVP due to acute right heart failure. Although arrhythmias such as JET may exist in such patients, normal CVP morphologic tracing would argue against this. Desaturation, although possible, is not consistently present during a pulmonary hypertension exacerbation unless a residual intracardiac shunt exists. Initial management includes increasing FiO_2 and inducing alkalemia with hyperventilation/sodium bicarbonate/THAM and ensuring adequate sedation/muscle relaxation. See PHTN section for ongoing management if not resolving.

3. B.
   Explanation: This patient's presentation is consistent with vocal cord paresis and aspiration. Recurrent laryngeal nerve damage is a known complication of aortic coarctation repair resulting in vocal cord dysfunction. These patients are at high risk of aspiration and feeding difficulties. To evaluate the vocal cords, a direct flexible laryngoscopy should be performed. Due to the strong suspicion of aspiration, the infant should also be evaluated by a speech therapist and a swallowing study may be needed to document the extent of aspiration and if thickened feeds can be provided safely.

4. B.
   Explanation: In this scenario, the infant with single ventricle physiology is presenting with signs of systemic hypoperfusion and low cardiac output syndrome. Remember that the single ventricular output is divided between the pulmonary and systemic circulations, leading to equal oxygen saturations in the pulmonary artery and the aorta. The amount of blood flowing to either the pulmonary circulation (Qp) or systemic circulation (Qs) is determined by the resistance to flow into these parallel circuits. In this case, the patient has pulmonary overcirculation with systemic hypoperfusion. Therefore, decreasing the FiO2 to 0.21 to raise the PVR is the best next step. Increasing the ventilator rate may further lower the PVR; thus allowing the pCO_2 to rise by lowering the ventilator rate may also be helpful. Pulmonary overcirculation is

commonly seen in patients with a low pulmonary vascular resistance and a low resistance Blalock–Taussig shunt (relatively large diameter and short length), as is the case with the infant in this scenario.

5. D.
Explanation: The patient has low cardiac output syndrome, associated with both low LAP and low Fontan circuit pressure; hypovolemia best explains these findings. If the systemic venous pressure is elevated and LA pressure is low, the differential diagnosis includes an increase in PVR, Fontan baffle obstruction or pulmonary artery stenosis. If both the systemic venous pressure and LA pressures are elevated, it could be related to one of the following causes: ventricular dysfunction, AV valve regurgitation or stenosis, cardiac tamponade, or arrhythmias.

Suggested Reading

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Cardiovascular Agents

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Contents

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Learning Objectives

- Review the physiology of autonomic nervous system receptors.
- Describe the various adrenergic receptors, their agonists, and their receptor relationship with G proteins.
- Summarize the clinical effects of specific adrenergic receptor-agonist interactions.
- Describe non-adrenergic mechanisms important in cardiovascular pharmacology.
- Summarize common factors that affect the pharmacokinetics of vasoactive infusions.
- Describe the physiology of vasodilators in the treatment of heart failure.
- Describe the mechanism of action, clinical uses, metabolism, and potential adverse effects of the following vasoactive agents:
  - Norepinephrine (NE)
  - Epinephrine (Epi)
  - Dopamine
  - Dobutamine
  - Phenylephrine
  - Isoproterenol (ISO)
  - Vasopressin
  - Milrinone
  - Nitroprusside
  - Nitroglycerine (NTG)
  - Novel cardiovascular agents
- Describe the mechanism of action, clinical uses, metabolism, and potential adverse effects of the following antihypertensive agents:
  - Nicardipine
  - Esmolol
  - Labetalol
  - Enalapril/enalaprilat
  - Fenoldopam
  - Phentolamine and phenoxybenzamine

20.1 Introduction

Cardiovascular agents are utilized when myocardial and/or circulatory dysfunction persists despite optimization of volume status. They have activity on the biochemical and neurochemical pathways that maintain and regulate vascular tone, cardiac contractility, and heart rate. Although these drugs may have multiple dose-dependent effects, they are often categorized by their primary cardiovascular activity. Terms used to describe the primary cardiovascular effect of these drugs are listed in Table 20.1.

Effective use of vasoactive agents requires understanding their mechanism of action and pharmacology in addition to the effects of the patient's endogenous response to their critical illness, which can modify the patient's response to the vasoactive agent. The observed action may differ from what is expected because of a host of factors that affect agonist-receptor interactions and post-receptor messaging within the cell. In addition, critical illness may affect drug clearance so that textbook effects associated with a specified infusion rate may not be observed at the bedside. Because of the variation in pharmacokinetics and pharmacodynamics of these agents, administration of vasoactive agents *should always be targeted to effect and not based on a fixed dose* (although for safety reasons a maximal dose may be considered for some agents, e.g., vasopressin).

Due to variation in pharmacokinetics, the patient's endogenous stress response and complex effects on secondary messenger systems within cells, vasoactive agents should be titrated to effect rather than based on a fixed dose.

Table 20.1 Primary cardiovascular effects, characteristics, and associated vasoactive agents

Primary cardiovascular effect	Characteristics	Example
Inotrope	Improves myocardial contractility and thus stroke volume	Dobutamine, epinephrine (Epi), norepinephrine (NE)
Vasopressor	Increases systemic and often pulmonary vascular resistance and blood pressure	NE, phenylephrine, vasopressin
Chronotrope	Increases heart rate	Epi, isoproterenol
Lusitrope	Improves rate and extent of diastolic relaxation which may decrease end-diastolic pressure	Milrinone, dobutamine, Epi
Vasodilator	Decreases systemic and/or pulmonary vascular resistance (afterload) and often decreases venous tone in capacitance vessels and thus end-diastolic pressure	Nitroprusside sodium, nitroglycerine, nitric oxide
Inodilator	Improves myocardial contractility while decreasing systemic and pulmonary afterload and often dilates venous capacitance vessels	Milrinone, levosimendan

In addition to agents used to support the cardiovascular system, various agents may be used in the PICU to manage severe, symptomatic hypertension. These agents typically block α- and/or β-adrenoceptors, calcium channels, and activation of the renin-angiotensin-aldosterone system (RAAS) or relax vascular smooth muscle by increasing intracellular cGMP. The pharmacology of several antihypertensive agents used to treat hypertensive emergencies will be reviewed in this chapter.

20.2 Physiologic Considerations of Vasoactive Agents

Cardiovascular agents often act at receptor sites within the autonomic nervous system; some agents affect intracellular metabolism of secondary message systems (e.g., milrinone and nitric oxide). When using vasoactive agents, it is often helpful to understand the autonomic receptor systems and subsequent receptor-induced biochemical pathways that affect myocardial function and vascular tone.

20.2.1 Overview of Adrenergic Receptor-Cell Interactions

In 1948, Alquist identified and classified adrenergic receptors, α and β, based on their differing response to pharmacologic agents. Since then, adrenergic receptor physiology has been the subject of extensive study. Techniques in molecular pharmacology lead to the classification of adrenergic and dopaminergic sub-subtypes (Fig. 20.1). The following section concentrates on adrenergic (α_1, α_2, β_1, β_2) and dopaminergic (DA_1, DA_2) receptor physiology.

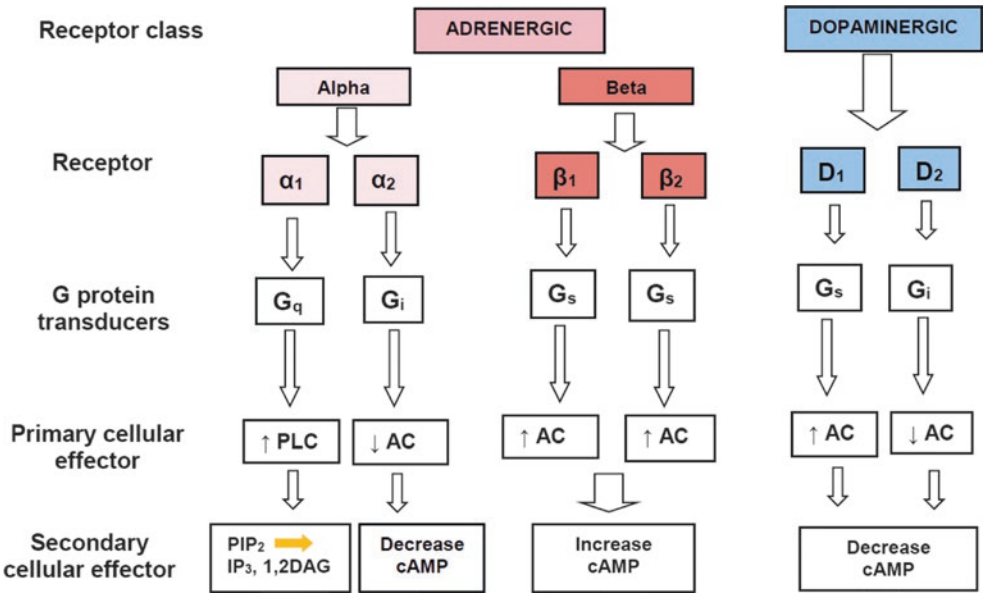

Fig. 20.1 Adrenergic and dopaminergic subtypes with respective G proteins and cellular effectors. *PLC* phospholipase C, *PIP2* phosphatidylinositol bisphosphate, *IP3* inositol triphosphate, *1,2 DAG* 1,2 diacylglycerol, *AC* adenylate cyclase, *cAMP* cyclic adenosine monophosphate

The α_1- and β_1-adrenoceptors are innervated by sympathetic nerves, whereas the α_2- and β_2-adrenoceptors are "hormonal" (or, in the case of presynaptic α_2-adrenoceptors, "autocrine") receptors. The hormonal adrenoceptor agonist is epinephrine (Epi), which is released by the adrenal gland, whereas norepinephrine (NE) is the neurotransmitter of the sympathetic nervous system (SNS) and acts as the principal physiologic agonist at α_1- and β_1-adrenoceptors.

The binding affinity of NE and Epi at the β_1-adrenoceptor is the same, but Epi has a significantly higher affinity than NE at the β_2-adrenoceptor. These differences in binding affinity and site of action explain why epinephrine has effects on heart rate and vascular resistance at plasma concentrations of 75–125 pg/mL, whereas the NE concentration required to observe a hemodynamic effect is approximately 1800 pg/mL. The difference in the plasma threshold concentration is explained by Epi acting at the hormonal β_2-adrenoceptor causing an increase in heart rate and fall in vascular resistance. Higher NE concentrations are needed for the agent to diffuse from the vascular space through the tissue to reach the innervated α_1- and β_1-adrenoceptors. Furthermore, there are two tissue uptake mechanisms designed to limit the effect of neuronally released NE from reaching the circulation that eliminate a portion of the exogenously administered catecholamines. These uptake systems reduce the quantity of infused catecholamines reaching the innervated receptors. These differences in receptor location have clinical implications with respect to the pharmacologic actions of vasoactive agents. For example, it explains why "low-dose" epinephrine infusions increase heart rate and vasodilate vascular beds, especially in the skeletal musculature; higher infusions are needed to subsequently raise vascular resistance when sufficient epinephrine reaches the vasoconstricting innervated α_1-adrenoceptors.

Adrenergic receptors (and various other vasoactive receptors) are tightly coupled to one of several different membrane-bound G proteins, which facilitate different actions within the cell depending on the receptor system. G proteins are composed of three subunits (α, β, γ) and are named for their association with guanosine diphosphate (GDP) and guanosine triphosphate (GTP). The inactive G-protein α subunit is bound to GDP; agonist binding to the adrenoceptor causes GTP to replace GDP on the α subunit. The activated GTP α subunit then separates from the $\beta\gamma$ subunit and acts on the target enzyme in either a stimulatory (Gs) or inhibitory (Gi) fashion. Depending on the cell, the

enzymes targeted by the activated G-protein α subunit include adenylate cyclase, phospholipase C, and phosphodiesterases. The activated α subunit may also directly act on potassium ion channels in vascular smooth muscle to cause hyperpolarization. Activation of the target enzyme also results in conversion of GTP back to the inactive GDP by GTPase coupled to the G α subunit.

Adenylate cyclase is the key enzyme involved in α_2, β_1, and β_2 signal transduction. When stimulated by the GTP α subunit, adenylate cyclase hydrolyzes ATP to the cytosolic second messenger 3,5-cyclic adenosine monophosphate (cAMP). A rise in intracellular cAMP concentration activates protein kinases that in turn phosphorylate biologically active proteins such as calcium channels. Increased intracellular cAMP and the subsequent phosphorylation of key proteins result in clinical effects depending upon the effector cell.

Adrenergic receptors (α_2, β_1, and β_2) are tightly coupled to membrane-bound G proteins that are composed of three subunits (α, β, γ). Depending on the structure of the α subunit, G proteins can stimulate (Gs) or inhibit (Gi) the membrane-bound adenylate cyclase.

At the α_1-adrenoceptor, Gq protein coupling stimulates the enzyme phospholipase C to hydrolyze phosphatidylinositol bisphosphate to intracellular second messengers: inositol triphosphate (IP_3) and diacylglycerol (DAG). The specific molecular mechanisms summarized below are based on the adrenoceptor-G protein relationships.

α_1 adrenoceptors are bound to a Gq protein that stimulates increased production of IP_3 and DAG as secondary messengers to increase vascular smooth muscle tone.

20.2.1.1 Adrenergic Receptor Density

The density of adrenoceptors on the cell surface may undergo regulation in response to agonist interactions with the receptor and may further be regulated by other mediators that are endogenously activated or exogenously given to treat critically ill children. Agonist stimulation of adrenoceptors causes receptor internalization and ultimately destruction; this reduces the response to agonists over time. Conversely, blocking agonist interaction with the receptor (e.g., with the use of beta-blockers) causes increased receptor density on the cell surface which explains why these blocking agents should generally be discontinued slowly to limit the risk of an excessive catecholamine response.

β-adrenoceptor expression on the cell surface is increased by corticosteroids, which may partly explain this agent's utility in children with asthma, especially if albuterol use reduced cell surface β-adrenoceptor density in the airways. Thyroid hormone increases the secondary messenger responsiveness to β-adrenoceptor stimulation, which explains the clinical symptoms observed in hyperthyroid patients. Conversely, inadequate thyroid hormone reduces the responsiveness to β-adrenoceptor agonists.

The density of adrenoceptors on the cell surface may undergo regulation in response to agonist interactions with the receptor and may further be regulated by other mediators that are endogenously activated or exogenously given to treat critically ill children.

Patients with chronic heart failure or other chronic stress states have increased endogenous SNS activity acting on adrenoceptors, which downregulates receptor expression. As expected, cardiac adrenergic receptor density is reduced in studies of explanted hearts in transplant recipients and cardiac biopsies during repair of acyanotic cardiac lesions.

20.2.1.2 Alpha- and Beta-Adrenoceptors

Alpha$_1$ (α_1)-Adrenoceptors

Key sites – α_1-adrenoceptors are innervated receptors primarily on vascular smooth muscle, but they are also found in the heart where activation increases contractility and stimulates cardiac muscle hypertrophy, although the effects on cardiac contractility are thought to be a minor effect. As noted in ► Chap. 15, Regional Circulation, the distribution of these receptors is not uniform; α_1-adrenoceptors are prominent in the skeletal muscle and renovascular and splanchnic circulation and less so in the cerebral and coronary circulation.

Binding – Ligand binding to α_1-adrenoceptors activates the Gα q subunit protein, which stimulates phospholipase C to hydrolyze phosphatidylinositol bisphosphate (PIP_2) to the intracellular second messengers: inositol triphosphate (IP_3) and 1,2 diacylglycerol (1,2 DAG). In vascular smooth muscle, IP_3 via a receptor-mediated process promotes the release of Ca^+ from the sarcoplasmic reticulum. 1,2 DAG activates protein kinase C, which causes an increased influx of extracellular calcium (Fig. 20.2). The net increase in cytosolic Ca^{+2} concentration ultimately causes vascular smooth muscle contraction.

α_1 vascular smooth muscle receptor binding acts on Gq protein, which releases GDP and binds GTP; the activated subunit then activates phospholipase C.

Phospholipase C hydrolyzes PIP_2 to IP_3 and 1,2 DAG, which produces IP_3 and 1,2 DAG, both mediators that promote increased intracellular Ca^+ which leads to vasoconstriction.

Alpha$_2$ (α_2)-Adrenoceptors

Key sites – α_2-adrenoceptors are present on presynaptic adrenergic and cholinergic nerve terminals. Peripheral α_2-adrenoceptors on vascular smooth muscle have also been identified and cause vasoconstriction when stimulated by agonists like epinephrine, but they are less prevalent than α_1-adrenoceptors. They are present in the central nervous system (CNS) vasomotor center of the medulla, the locus coeruleus, and the dorsal spinal column.

Binding – Binding of presynaptic α_2-adrenoceptors by synaptically released NE starts an autocrine negative feedback loop that decreases NE release (Fig. 20.3). Presynaptic receptor binding activates G_i protein that inhibits adenylate cyclase and thus decreases cAMP formation. Reduced intracellular cAMP reduces protein kinase A activity, which decreases downstream phosphorylation of proteins important in NE release. Although exogenous Epi and NE binds at the presynaptic α_2-adrenoceptor, the direct effect of these agents on vascular smooth muscle adrenoceptors dominate the pharmacologic response.

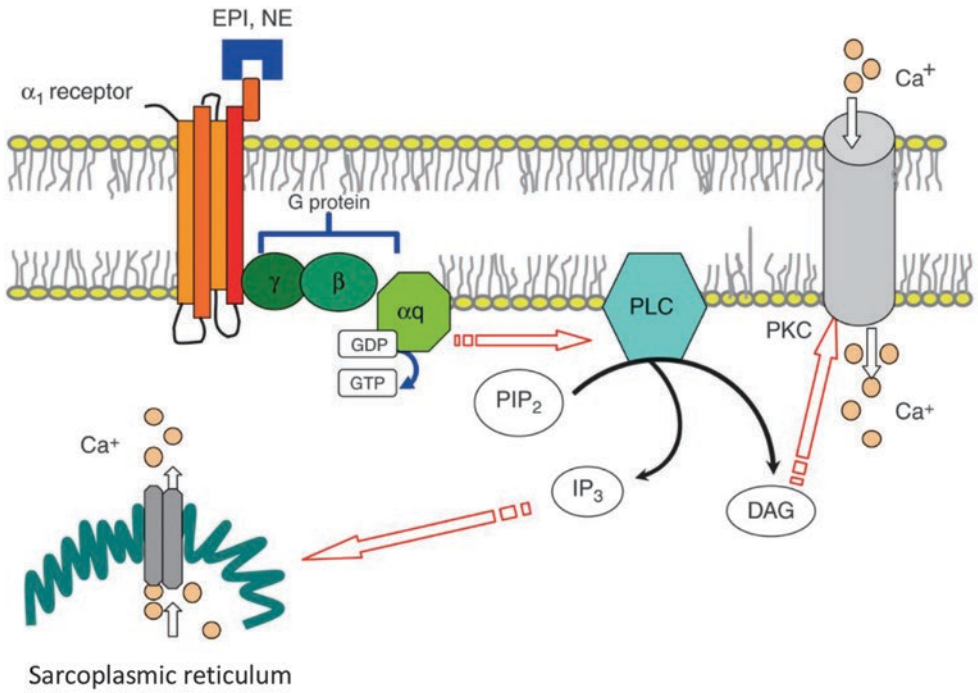

Fig. 20.2 Vascular α_1-adrenoceptor binding by agonists such as epinephrine (EPI) and norepinephrine (NE) results in a G-protein conformational change that releases GDP and binds GTP. The activated α q subunit of the G protein stimulates phospholipase C (PLC) to hydrolyze phosphatidylinositol bisphosphate (PIP2) to the second messengers: inositol triphosphate (IP3) and 1,2 diacylglycerol (DAG). These second messengers promote an increase in cytosolic calcium concentration which results in vascular smooth muscle contraction. IP3 promotes the release of Ca^+ from the sarcoplasmic reticulum, and 1,2 DAG activated protein kinase C (PKC) causes influx of extracellular calcium

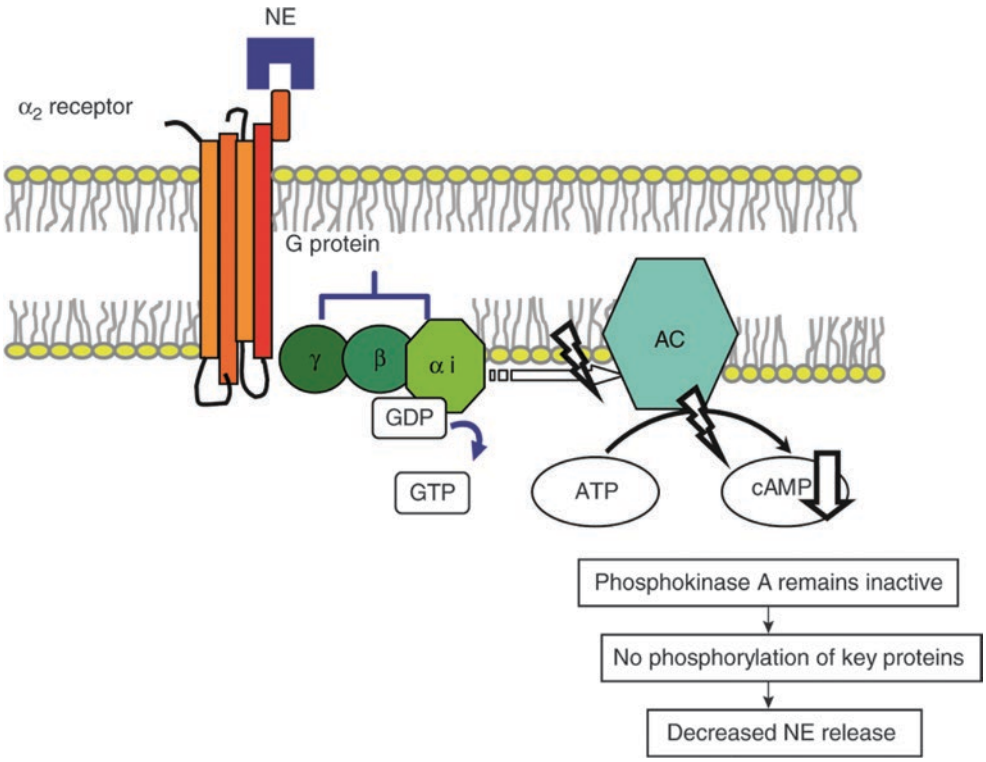

Fig. 20.3 α_2 presynaptic adrenoceptor binding inhibits adenylate cyclase activity, which decreases the intracellular cAMP concentration and ultimately decreases NE release

Presynaptic α_2-adrenoceptor nerve terminal binding acts on the Gi protein, which releases GDP and binds GTP ⇒ inhibition of adenylate cyclase ⇒ decreased cAMP ⇒ decreased protein kinase activity ⇒ inhibition of NE release.

In the CNS, α_2-adrenoceptor agonists, such as clonidine and dexmedetomidine, reduce sympathetic nervous system (SNS) activity, which leads to vasodilation and reduced heart rate and contractility (if increased from baseline). Binding of α_2-adrenoceptors located in the dorsal column of the spinal cord and the locus coeruleus of the brainstem also has sedative and analgesic effects.

Beta$_1$ (β_1)-Adrenoceptors

Key sites – β_1-adrenoceptors are located in the myocardium and kidney. Within the heart, β_1-adrenoceptors are found in the atria and ventricles and throughout the conduction system.

Binding – Ligand binding to β_1-adrenoceptors activates Gs protein which stimulates adenylate cyclase. Increased adenylate cyclase activity increases cytosolic cAMP. Increased cAMP levels activate protein kinase A, which increases the phosphorylation of target proteins. These targets include myocardial myofilament proteins and Ca^+ channel proteins. Ca^+ influx through membrane-bound channels ensues and results in a *net increase* in cytosolic calcium. Clinically, this leads to increased actin-myosin coupling and ultimately increased inotropy (Fig. 20.4).

It is important to appreciate that the net increase in cytosolic calcium not only increases myocardial inotropy during systole but also has implications on muscle relaxation during diastole. Lusitropy, which is the rate at which myocardial relaxation occurs, is also affected by cytosolic Ca^+ gradient changes. Increased cytosolic Ca^+ increases the rate of Ca^+ reuptake into the sarcoplasmic reticulum, which potentiates diastolic relaxation. In addition, protein kinase A phosphorylation of myofilament proteins enhances the lusitropic response by promoting a reduction in myofilament tension.

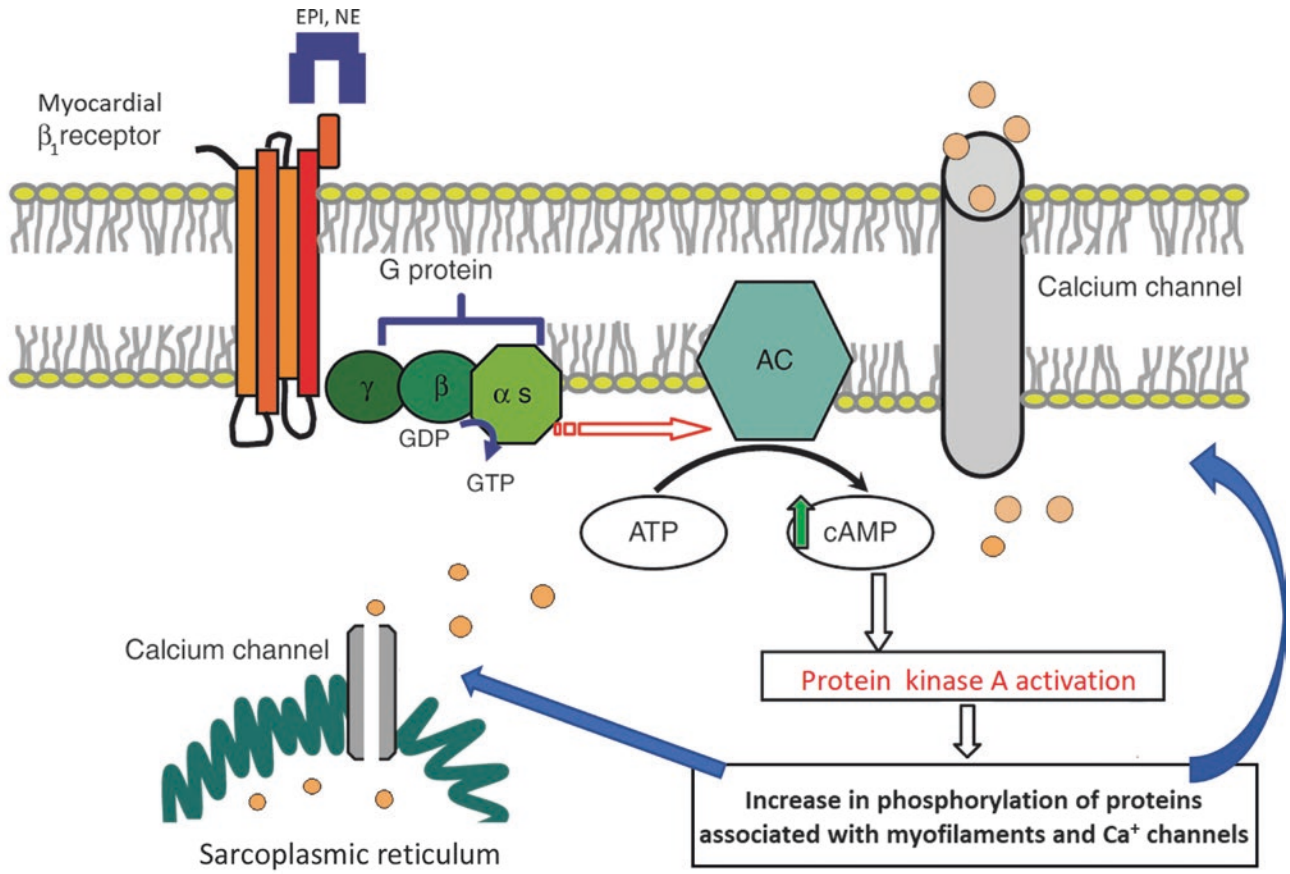

Fig. 20.4 Myocardial β_1-adrenergic G-protein signal transduction. Ligand binding (e.g., *EPI*, *NE*) to β_1 adrenoceptors on myocardium results in adenylate cyclase (*AC*) activation via Gs-protein activation. Increased AC activity increases cAMP, which increases protein kinase A activity, which increases phosphorylation of proteins associated with myofilaments and Ca^+ channels. Membrane calcium channel stimulation results in Ca^+ influx into the cytosol and increases reuptake of Ca^+ into the sarcoplasmic reticulum (SR). Clinically, increased cytosol Ca^+ concentration results in increased inotropy, lusitropy, and chronotropy

Increased lusitropy also facilitates an increased heart rate as less time is required for passive filling by increasing the rate of calcium reuptake, and it makes more calcium available in the sarcoplasmic reticulum, which facilitates increased contractility by providing a pool for rapid release of calcium into the cytoplasm. In cardiac pacemaker cells, increased cAMP also increases their activation rate (i.e., chronotropy).

Beta$_2$ (β_2)-Adrenoceptors

Key sites – β_2-adrenoceptors are located on the surface of vascular smooth muscle (skeletal, coronary, gastrointestinal), ciliary muscle, bronchial smooth muscle, lymphocytes, and mast cells. They also are located in both the atria and ventricles in a ratio of β_1- to β_2-adrenoceptors of approximately 70:30 in the atria and 80:20 in the ventricle.

Binding – Ligand binding to β_2-adrenoceptors activates Gs protein, which stimulates adenylate cyclase leading to increased cAMP and increased protein kinase A activity. However, unlike cardiac myocyte β_1-adrenoceptor stimulation, increased cAMP in vascular smooth muscle increases the uptake of cytosolic calcium by the sarcoplasmic reticulum and increases efflux of calcium out of the cell resulting in a net decrease in cytosolic calcium. Increased cAMP in

Myocardial β_1-adrenoceptor binding ⇒ activation of Gs protein ⇒ adenylate cyclase stimulated ⇒ increased cAMP ⇒ increased protein kinase A activity ⇒ increases phosphorylation of proteins associated with Ca+ channels and cardiac contractile proteins ⇒ increased inotropy, lusitropy, and chronotropy.

vascular smooth muscle also inhibits myosin light-chain kinase activity, which is responsible for phosphorylating smooth muscle myosin. Therefore, β_2 agonists inhibit smooth muscle contraction and promote smooth muscle relaxation (vasodilation, bronchodilation).

In the heart, atrial β_2-adrenoceptors, which are hormonal receptors, increases the pacemaker rate, which partly explains why a selective β_2 agonist such as albuterol causes tachycardia. Similarly, low-dose infusions of epinephrine cause tachycardia with less effect on contractility, which requires higher epinephrine concentrations to activate cardiac β_1 adrenoceptors.

Ligand binding (e.g., Epi, ISO) to β_2-adrenoceptors on vascular or bronchial smooth muscle results in activation of adenylate cyclase via Gs protein. Adenylate cyclase activity results in increased cAMP, increased protein kinase activity, and increased phosphorylation of proteins associated with Ca+ channels. Unlike β_1 receptor stimulation on the myocyte, β_2 receptor stimulation on vascular and bronchial smooth muscle increases the uptake of cytosolic calcium by the sarcoplasmic reticulum and pumps calcium out of the cell leading to a net decrease in cytosolic calcium. Clinically, the decreased cytosolic calcium results in vascular and bronchial smooth muscle relaxation.

20.2.1.3 Dopamine Receptors

Dopamine is a neurotransmitter that is generally more important in the central versus the peripheral nervous system. Dopamine is an intermediary in the pathway for NE and Epi synthesis and is only released as a neurotransmitter by select sympathetic nerves located in the kidney and splanchnic vascular bed as well as the anterior pituitary gland and hypothalamus (◘ Fig. 20.5). Although dopamine receptors are in the renal and splanchnic vascular beds, their clinical significance is uncertain since the anticipated beneficial effects of infusing dopamine or dopamine receptor agonists have had limited clinical utility.

Exogenous dopamine can interact with adrenergic receptors in a dose-dependent fashion but has a lower binding affinity than Epi or NE. Instead, studies show that much of dopamine's cardiovascular action is mediated by stimulating NE release from sympathetic nerves. Since NE stored in sympathetic nerve terminals is depleted in chronic heart failure and other chronic stress states, dopamine has limited inotropic effects in these settings. In the peripheral vascular system, dopamine interacts with a group of distinct dopaminergic receptors, most importantly dopamine$_1$ (DA_1) and dopamine$_2$ (DA_2) receptors.

Dopamine$_1$ (DA_1)

DA1 receptor binding results in Gs protein activation of adenylate cyclase, which increases cAMP production and protein kinase activity causing vasodilation of selective vascular beds.

Key sites – Like α_1- and β_1-adrenoceptors, DA_1 adrenoceptors are innervated receptors present in renal, mesenteric, and coronary vascular smooth muscle. Non-innervated DA_1 receptors are on the surface of proximal renal tubule cells.

Binding – Ligand binding activates Gs protein, causing vasodilation of selective vascular beds. Locally produced dopamine acts as an autocrine/paracrine natriuretic hormone by inhibiting the activity of both apical (e.g., Na^+/H^+ exchange, Cl^-/HCO_3^- exchange, and Na^+/Pi cotransport) and basolateral (e.g., Na^+, K^+-ATPase, and Na^+/HCO_3^- cotransport) tubule transporters. These actions facilitate increased salt and water excretion.

Dopamine$_2$ (DA_2)

Key sites – Like α_2- and β_2-adrenoceptors, DA_2 receptors are found on presynaptic nerve terminals and in the adrenal cortex. They are also found in the anterior pituitary gland and other CNS locations.

Binding – Similar to presynaptic α_2-adrenoceptors, presynaptic DA_2-receptor stimulation inhibits NE release from the sympathetic nerve terminus. Similar effects are observed at DA_2 receptors in the CNS; the effect is mediated by activation of Gi protein, which decreases cAMP. DA_2 receptor activation of cells in the anterior pituitary inhibits release of TSH and prolactin. In the adrenal cortex, DA_2-adrenoceptor stimulation inhibits aldosterone synthesis and release.

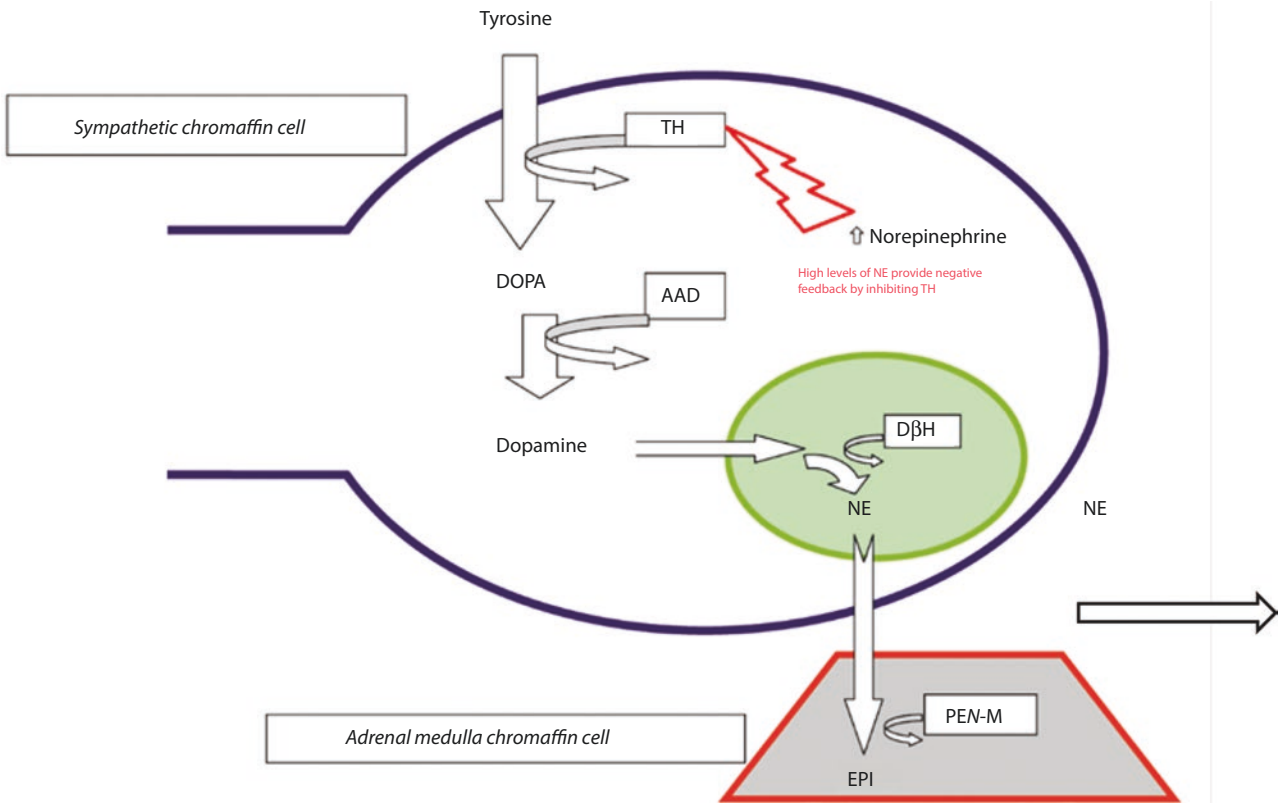

Fig. 20.5 Dopamine is an intermediary in norepinephrine (NE) and epinephrine (EPI) biosynthesis. Tyrosine is converted to dihydroxyphenylalanine (DOPA) by the rate-limiting enzyme, tyrosine hydroxylase (TH). High levels of NE inhibit TH. DOPA is decarboxylated by aromatic amino acid decarboxylase (AAD) to produce dopamine. Dopamine enters the storage vesicle and is β-hydroxylated by dopamine β-hydroxylase (DβH) to produce NE. Approximately 85% of NE synthesized in the adrenal medulla is converted to EPI by phenylethanolamine *N*-methyltransferase (PE *N*-M)

The relationship between sympathomimetic agents and adrenoceptors including dopamine receptors are summarized in Table 20.2.

20.2.1.4 Genetics of Adrenoceptors

Another source of variation in clinical response to adrenergic agonists was identified after receptor sequencing became available. Single-nucleotide polymorphisms (SNP) have been mostly studied for the β_2-adrenoceptors, which explains some of the variation in response to β_2 agonists observed in asthmatic patients. For example, one SNP is associated with a threefold to fourfold reduction in the maximal stimulation of adenyl cyclase activity. This SNP is associated with a smaller increase in heart rate, contractility, and plasma renin activity in response to dobutamine infusion in healthy young subjects and was associated with the need for a higher dose and longer inotrope support after CABG in patients who were treated with metoprolol preoperatively. Another SNP is associated with rapid β_2-adrenoceptor internalization reducing responsiveness to ongoing agonist stimulation.

Single-nucleotide polymorphisms of adrenergic receptors likely explain some of the variation in response to adrenergic agonists observed in clinical use.

20.2.1.5 Complexity of Adrenoceptor Activation

Adrenergic signal transduction results in a myriad of physiologic responses including highly complex metabolic processes. Adrenergic receptor-mediated cellular and hemodynamic effects in response to endogenous and exogenous agonists are summarized in (Table 20.3).

Table 20.2 Relative receptor stimulation by sympathomimetic agents

Sympathetic agent	Relative receptor action[a]	Quantitative receptor action
Sympathomimetics:		
Norepinephrine	$\alpha_1 = \beta_1 >> \beta_2$	++++ α_1, ++++ β_1
Epinephrine	$\beta_2 > \beta_1 = \alpha_1$	++ α_1, ++++ β_1, ++++ β_2
Phenylephrine	α_1 selectively	++++ α_1
Isoproterenol	$\beta_1 = \beta_2$	++++ β_1, ++++ β_2
Dopamine		
Low dose[b]	$DA_1 > \beta_1 > \alpha_1$	+++DA_1
Intermediate dose	$\beta_1 > \alpha_1 > DA_1$	++ α_1, ++ β_1
High dose	$\alpha_1 >> \beta_1 > DA_1$	++++ α_1, ++ β_1
Dobutamine: (+) isomer (−) isomer	 $\beta_1 \cong \beta_2$, α_1 *antagonist* Weak β_1 and β_2 agonist, α_1 *agonist*	 ++++ β_1, ++ β_2 Variable effect on α_1 depending on balance of agonist/antagonist actions
Alpha-blockers:		
Phenoxybenzamine	α_1, α_2	Irreversible receptor inhibition
Phentolamine	α_1, α_2	
Prazosin	α_1	
Beta-blockers:		
Propranolol	β_1, β_2	Equal effects at β_1, and β_2
Esmolol, Atenolol, Metoprolol	β_1	
Labetalol	β_1, α_1	β_1 inhibition is 7 times greater than α_1 blockade

[a]Relative receptor action accounts for the differences in adrenoceptor location such that the hormonal adrenoceptors (β_2 and α_2) are activated at lower drug concentrations than the innervated receptors (β_1 and α_1)
[b]"Low-dose" assumes normal pharmacokinetics. Dopamine is a weak direct agonist at α_1- and β_1-adrenoceptors; much of its action is mediated by facilitating the release of NE from sympathetic nerves

20.2.1.6 Phosphodiesterase Inhibition

Inhibition of phosphodiesterase III causes a sustained increase in the cAMP levels, leading to increased protein kinase A activity and ultimately increased myocardial cytosolic calcium and decreased vascular smooth muscle cytosolic calcium. The net clinical effect is increased inotropy combined with vasodilation in both the systemic and pulmonary circulations as well as reduced tone in the venous capacitance system.

Since cAMP is an essential mediator in the sympathetic response, inhibition of its breakdown has important clinical implications. Phosphodiesterase III is responsible for the breakdown of cAMP; thus, phosphodiesterase III inhibition in the myocardium and vascular smooth muscle leads to sustained cAMP levels and increased protein kinase A activity. The ultimate effect on cytosolic calcium concentration is cell type-dependent; calcium release is increased in myocardial cells and decreased in vascular smooth muscle (Fig. 20.6). In smooth muscle, phosphorylation of myosin light-chain kinase by protein kinase A inhibits its activity, which is essential for smooth muscle contraction. Milrinone (see below) is the most commonly utilized phosphodiesterase III inhibitor. The net clinical effect of milrinone is increased inotropy with vasodilation, often referred to as inodilation.

Table 20.3 Relationship of agonists to adrenergic receptors, intracellular messengers, cellular response, and hemodynamic response

Agonists	Receptor	G protein	Second messenger	Cellular response	Hemodynamic result
Epinephrine Norepinephrine Phenylephrine Dobutamine[a]	α_1	Gq	IP_3, 1,2DG ⇧	Smooth muscle: Increased cytosolic Ca^+	Vasoconstriction
Norepinephrine Epinephrine Dobutamine Clonidine, Dexmedetomidine	α_2	Gi	cAMP ⇩	Central and peripheral presynaptic adrenergic nerve terminals: Decreased norepinephrine release from sympathetic nerves (negative feedback)	Any action of exogenous NE, Epi, and Dob at presynaptic α_2- adrenoceptors is overwhelmed by the vasoconstriction effect of these agents at the α_1 receptor Central α_2 agonists lead to sympatholytic effects
Epinephrine Isoproterenol Dobutamine Norepinephrine Dopamine	β_1	Gs	cAMP ⇧	Myocardium: Increased influx of Ca^+ through membrane channels, increased Ca^+ release from sarcoplasmic reticulum, and increased Ca+ reuptake into the sarcoplasmic reticulum Kidney: Increased renin production	Increased inotropy, lusitropy, and chronotropy Increased renin-angiotensin-aldosterone activity
Isoproterenol Epinephrine Dobutamine	β_2	Gs	cAMP ⇧	Smooth muscle: Increased removal of cytosolic Ca^+ from cytoplasm and into sarcoplasmic reticulum	Vasodilation Bronchodilation
Dopamine Fenoldopam	DA_1	Gs	cAMP ⇧	Renovascular, splanchnic, and coronary smooth muscle: Increased PKA activity Increased Ca^+ mobilization	Selective vasodilation

[a]Dobutamine has a unique pharmacologic action due to opposing actions of the two isomers on α_1-adrenoceptor resulting in mainly β-adrenoceptor stimulation. In addition, a long-lasting active metabolite has α_1 antagonist activity. PKA is protein kinase A

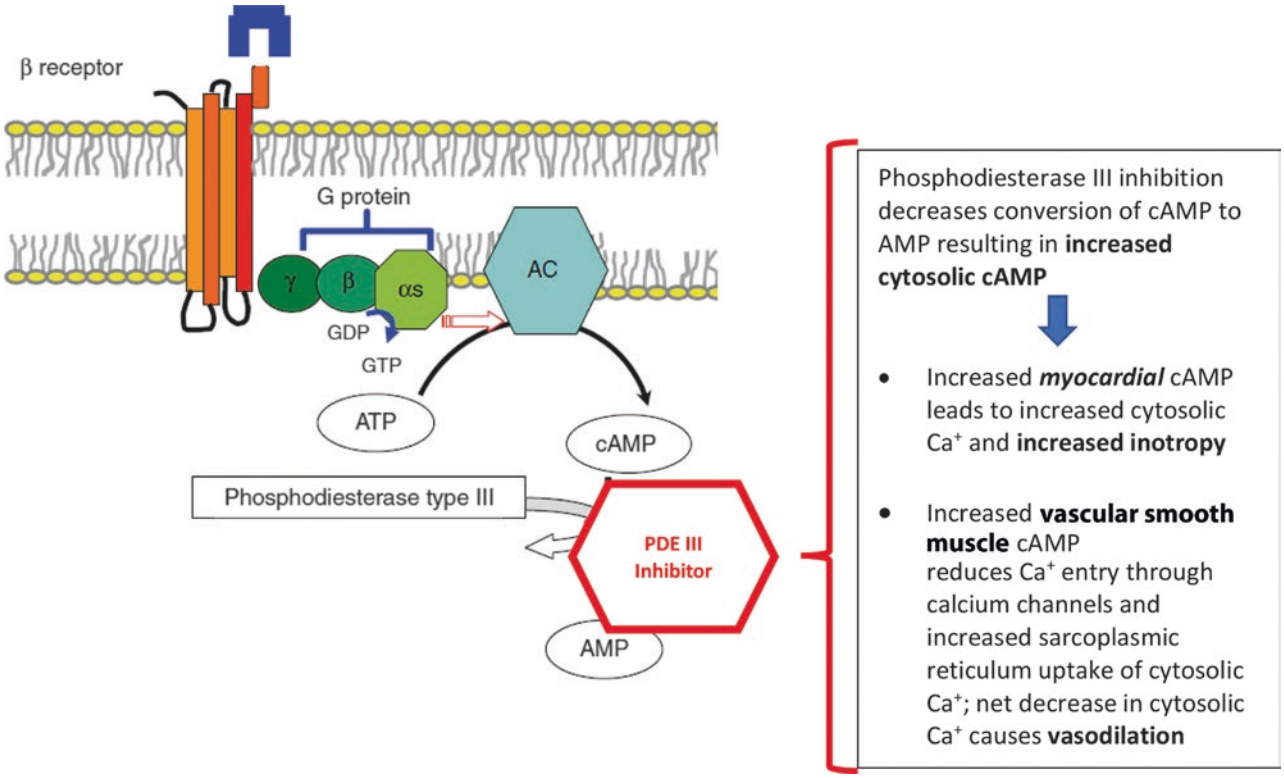

Fig. 20.6 Inhibition of phosphodiesterase III (e.g., milrinone) causes a sustained increase in cAMP levels, protein kinase A activity, and ultimately increased myocardial cytosolic calcium concentration but decreased vascular smooth muscle cytosolic calcium. The net clinical effect is inodilation

20.2.2 Pharmacokinetics of Vasoactive Infusions

Because of the short half-life for most of the vasoactive agents, they are administered as a continuous infusion. One implication is that changes in infusion rate will rapidly achieve a new steady-state concentration; 90% of the steady-state concentration is achieved in three half-lives, which is on the order of 6–9 minutes for the sympathomimetic drugs.

Pharmacokinetic studies of sympathomimetic agents identified both age-based and disease-based variations in clearance. In general, younger children clear these agents more rapidly than older children and adolescents; neonates tend to clear these agents more slowly, especially premature infants. More importantly, wide interindividual variation in clearance is observed in critically ill infants and children based on studies using dopamine, dobutamine, norepinephrine, or epinephrine. Low clearance is associated with renal and/or hepatic dysfunction and low cardiac output states; the latter likely impairs clearance due to reduced blood flow to the kidney and liver, which are the main sites for metabolic elimination. Clearance may vary up to 10- to 20-fold so that an infusion of dopamine or dobutamine at 2 mcg/kg/min in one child may achieve the same steady-state concentration seen in another child receiving an infusion at 20 mcg/kg/min!

The pharmacokinetics of nitroprusside and nitroglycerine do not exhibit the same variations in clearance since their clearance is not dependent on liver or renal function. Milrinone, however, is renally cleared and has a long half-life in normal individuals (~1.5–2.5 hour). Thus, a change in infusion rate will not achieve 90% of the new steady-state concentration for at least 3–4.5 hours and may be much longer in an infant or child with reduced renal function. Thus, the onset of the beneficial or adverse effect of the drug may be quite delayed after a change in infusion rate.

There are wide variations in the clearance of sympathomimetic agents observed in infants and children. Reduced renal and/or liver function and low cardiac output states reduce clearance. Thus, a given infusion rate may produce markedly different effects in individual patients.

20.2.3 Pharmacodynamics of Vasoactive Infusions

The preceding discussions regarding changes in receptor density, expression, genetic variation, and secondary messenger activation are several factors that affect the clinical manifestation observed from a vasoactive drug infusion. Innate physiologic stress responses are also very important to consider when understanding the effects of vasoactive infusions.

Critically ill or injured children typically mount an endogenous stress response with increased SNS activation and elevated endogenous Epi concentrations. Corticosteroid concentrations are often increased along with vasopressin levels. In addition, multiple other mediator signals are either stimulating or inhibiting endothelial signaling with the release of NO, endothelial-derived hyperpolarizing factor, or other mediators. Vascular smooth muscle cells have multiple surface receptors that either increase or decrease secondary messengers (see ◘ Fig. 20.7), which then either stimulate or inhibit the action of various enzymes and channels within the cell. The balance between these conflicting signals ultimately leads to the net vascular tone. All forms of shock, but especially septic shock, may be characterized by vasoplegia where factors that reduce actin-myosin coupling overwhelm the vasoconstricting mediators. Similar conflicting intracellular signals are present in the cardiomyocytes of critically ill children.

Nitroprusside and nitroglycerine exhibit much less variation in pharmacokinetics, whereas milrinone is renally excreted with a relatively long half-life meaning that changes in the infusion rate do not reach a new steady-state concentration for many hours.

There are complex mechanisms that regulate vascular smooth muscle tone. Multiple mediators act on receptors or enzyme systems generating secondary and tertiary intracellular messengers that affect vascular smooth muscle tone, making it unlikely that a given vasoactive agent will produce a consistent response in different patients.

The physiologic effects from vasoactive infusions also depend on the target organ. As reviewed in ▶ Chap. 15, Regional Circulation, the density and type of adrenergic receptor varies by organ system. For example, cutaneous blood vessels physiologically express mainly α_1-adrenoceptors; thus, NE and Epi cause cutaneous vasoconstriction. Conversely, the cerebral and coronary vasculatures have a low density of adrenoceptors and are not prone to the vasoconstrictive effects of α_1 stimulation. Skeletal muscular vasculature has a high concentration of β_2-adrenoceptors, so epinephrine markedly increases skeletal muscle blood flow, whereas NE has little effect at these receptors. This may explain the observation in animal and clinical studies that Epi tends to increase cardiac output but may compromise splanchnic perfusion by "stealing" blood flow to skeletal muscles, whereas NE tends to maintain splanchnic perfusion in septic shock.

In addition to the polymorphisms in β-adrenoceptors, a recent review identified 24 genes associated with significant differences in outcome in sepsis and/or cardiovascular disease. These genes regulate various inflammatory mediators, signaling pathways and channels. This adds further complexity to the pharmacodynamics of vasoactive infusions.

Ultimately, the net effect of a vasoactive agent on a target cell depends on the balance of conflicting messages being received by the cell. When combined with the variations in pharmacokinetics noted above, it should not be surprising that there may be wide variation in the hemodynamic response to a vasoac-

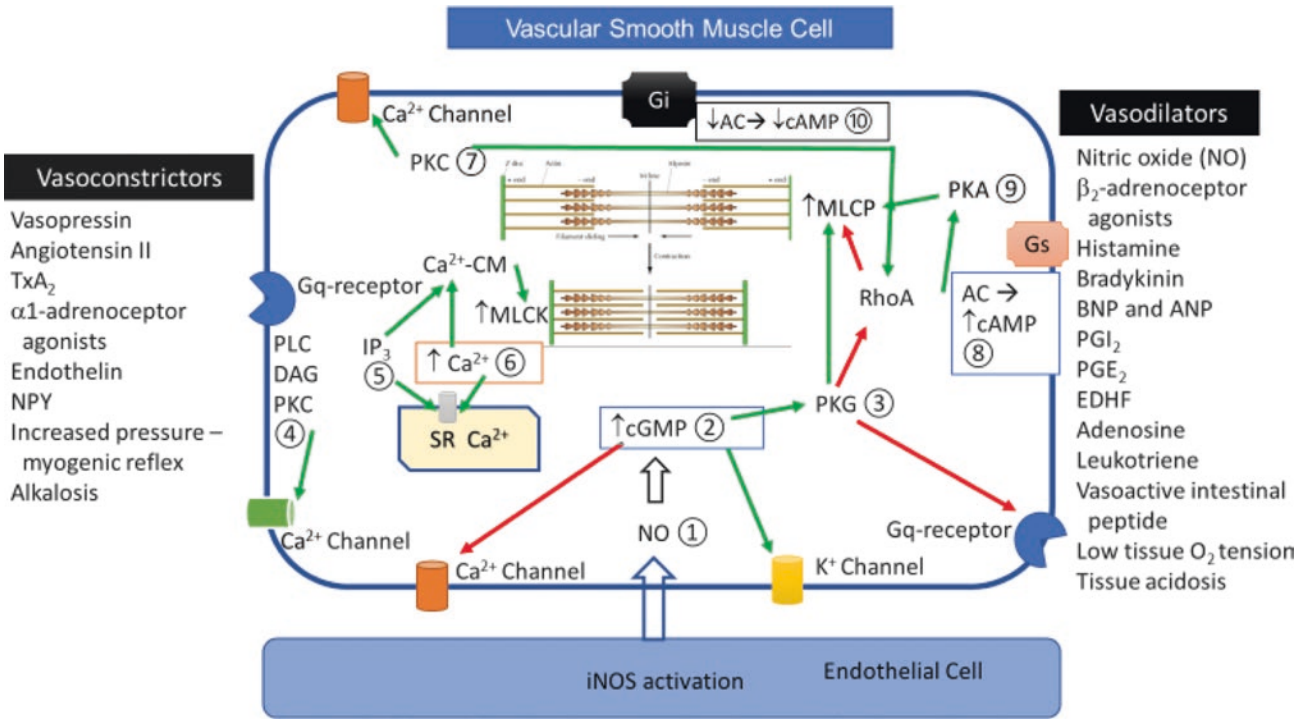

Fig. 20.7 A portion of the complex factors affecting vascular tone are illustrated. A host of mediators stimulate either smooth muscle contraction or relaxation through action at specific G-protein-coupled receptors. ① Nitric oxide (NO) is derived from endothelial cells under a variety of stimuli. Inducible nitric oxide synthase (iNOS) is an important source of increased NO production; in sepsis models, NO production increases more than 1000-fold. NO activates soluble guanylate cyclase to increase cGMP production. ② cGMP inhibits (red arrow) the opening of voltage-gated Ca^{2+} channels and opens a specific K+ channel leading to hyperpolarization, which reduces intracellular Ca^{2+}. ③ cGMP activates protein kinase G (PKG), which phosphorylates RhoA and other proteins (not shown); RhoA phosphorylation inhibits RhoA's inhibitory effect on myosin light-chain phosphatase (MLCP). PKG also phosphorylates and thus activates MLCP, which reduces actin-myosin coupling. ④ When a vasoconstricting agonist binds to the Gq-coupled G-protein receptor complex, phospholipase C (PLC) is activated, which generates 1,2-diacylglycerol (DAG) and 1,4,5-inositol triphosphate (IP_3). DAG activates protein kinase C (PKC), which phosphorylates a number of kinases (not shown) with the net effect of increasing actin-myosin interaction and thus smooth muscle contraction; IP_3 also increases the activity of the Ca^{2+}-calmodulin complex. The α_1-Gq adrenoceptor complex opens a receptor-operated calcium channel increasing intracellular Ca^{2+} concentration. ⑤ IP_3 opens a channel on the sarcoplasmic reticulum (SR) to release stored Ca^{2+} into the cytoplasm. ⑥ Increased intracellular Ca^{2+} concentration increases the interaction with calmodulin (CM); the Ca^{2+}-CM complex activates myosin light-chain kinase (MLCK), an important enzyme that increases actin-myosin coupling. ⑦ PKC also opens voltage-gated Ca^{2+} channels increasing the intracellular Ca^{2+} concentration. ⑧ When a vasodilating agonist binds to its Gs-coupled receptor, adenylate cyclase (AC) is activated, which increases cAMP production. ⑨ cAMP activates protein kinase A (PKA); among its actions, PKA activates MLCP, which reduces actin-myosin coupling. In addition, PKA phosphorylates MLCK, which inhibits its activity (not shown). ⑩ Agonist binding to α_2-Gi-coupled adrenoceptors inhibits adenylate cyclase, reducing cAMP production. Red arrows show inhibitory pathways; green arrows activate the target. There are several different Ca^{2+} and K^+ channels which are regulated by kinases and phosphatases (not shown). EDHF is endothelial-derived hyperpolarizing factor; TxA_2 is thromboxane; NPY is neuropeptide Y; BNP and ANP are B-type and atrial natriuretic peptides, respectively; PGI_2 is prostacyclin; PGE_2 is prostaglandin E_2

tive infusion. In addition, clinicians should be aware of how other therapeutic interventions may modulate the patient's response. For example, using sedative agents reduces the patient's SNS response, which may result in the need for a higher vasoactive infusion rate; conversely, as sedation is withdrawn, the patient often needs less vasoactive support. Giving corticosteroids increases the expression and responsiveness at β-adrenoceptors; thus, a lower inotrope infusion may be required. Finally, it is important to recognize that critical illness is a dynamic process; thus, the patient's endogenous response and local mediator production in addition to changes in organ function and blood flow (i.e., changes in drug pharmacokinetics) will impact the pharmacodynamics observed. Textbook infusion rates are helpful starting points for an infusion, but clinicians need to be aware of how alterations in organ function and the

patient's stress response may modulate the response; ultimately the patient's response is the most important determinant of either beneficial or harmful effects.

20.3 Specific Agents and Clinical Indications

20.3.1 Norepinephrine

20.3.1.1 Pharmacology

Norepinephrine (NE) is the principle neurotransmitter of the SNS. Like other catecholamines, NE is degraded in the liver and kidney by methylation via catechol-O-methyltransferase (COMT) or by deamination via monoamine oxidase (MAO). NE is also cleared from the circulation by reuptake at nerve terminals (uptake-1) and in nonneuronal tissues by uptake-2. It has a short half-life of 2–2.5 minutes. The usual dosage range for NE is 0.01–1 mcg/kg/min.

20.3.1.2 Clinical Effects

NE is a potent adrenergic agonist acting primarily on the α_1- and β_1-adrenoceptors with little effect at β_2-adrenoceptors, so it increases systemic vascular resistance, mean arterial pressure, and myocardial oxygen consumption (MVO_2) while stimulating increased inotropy. Many reviews and textbooks state that NE is a weak inotrope. This is based on studies showing that it may not increase cardiac output when blood pressure is increased. However, these actions on cardiac output are due to the effect of NE to increase blood pressure, which activates the baroreceptor reflex resulting in a reduced heart rate. The increased afterload from its peripheral vascular effects also limit the increased stroke volume expected from its inotropic effect. Recall that NE is the neurotransmitter released at the myocardial innervated β_1-adrenoceptors, and thus it is expected to have significant inotropic effects. In patients with hypotension or low blood pressure and cardiac output, especially patients with evidence of vasoplegia, the baroreceptor reflex is not stimulated by an NE-induced increase in systemic vascular resistance; thus, NE-mediated inotropic effects increase stroke volume and cardiac output.

NE has a reduced chronotropic effect compared with Epi since it has weak action at the atrial β_2-adrenoceptors. It also increases venous tone, which may increase end-diastolic pressure and MVO_2. NE may increase PVR, especially in patients with increased pulmonary vascular muscularization. Historically its use was limited by fear of mesenteric and renal ischemia; however, recent evidence suggests its use in septic patients after volume resuscitation may restore perfusion to susceptible vascular beds by reestablishing mean arterial pressure. In addition, norepinephrine may promote synthesis of prostaglandins that attenuate renal afferent arteriolar vasoconstriction.

In cardiogenic shock, NE is considered the drug of choice. A recent multicenter clinical trial comparing NE to Epi in adults with postinfarction cardiogenic shock was stopped prematurely because of a significant increase in mortality and refractory shock in the Epi arm.

Norepinephrine is an excellent pressor choice for shock states characterized by excessive vasodilation. Although often considered only a vasoconstrictor, NE possesses potent inotropic activity at the myocardial β_1-adrenoceptor.

Low binding affinity for β_2-adrenoceptors limits the chronotropic effects of NE.

20.3.1.3 Clinical Indications

NE like all other vasoactive agents should be used only when intravascular volume is adequate. Clinical conditions appropriate for its use include:

- Hyperdynamic (i.e., vasodilated) septic shock
- Neurogenic shock
- Cardiogenic shock
- Tricyclic antidepressant toxicity producing shock

20.3.1.4 Adverse Effects

NE increases MVO_2 by increasing contractility, afterload, and ventricular end-diastolic pressure. Since NE does not act at atrial β_2-adrenoceptors, it has little effect on heart rate, which also may be suppressed if the increase in SVR increases the blood pressure and reflexively increases vagal activity. Improper use of NE (i.e., without adequate volume loading) decreases end-organ perfusion leading to ischemia, especially in the kidney and gut. Like other α-adrenergic agonists, NE increases tone in the venous system, which increases mean systemic pressure that facilitates increased venous return. Since the normal pulmonary vasculature has limited muscularization (see ▶ Chap. 15: Regional Circulation), NE often has little effect on PVR, but in a patient with pulmonary hypertension and/or increased muscularization of the pulmonary vasculature, NE will increase pulmonary vascular resistance and thus increase right ventricular afterload. Due to the sparsity of cerebral vascular and coronary adrenoceptors, these circulations are at reduced risk from the vasoconstrictor effects of NE.

Although NE is often considered a vasoconstrictor, it is the neurotransmitter released from sympathetic nerves and thus has high affinity for cardiac β_1-adrenoceptors. Therefore, it produces inotropic actions in addition to increasing vascular resistance. NE has little effect at β_2-adrenoceptors so there is little effect on the atrial pacemaker. In cardiogenic shock, adult studies show that NE is superior to Epi.

Extravasation can lead to severe tissue necrosis; therefore, infusion should be limited to central venous sites. Local extravasation can be treated by infiltrating the α-adrenergic antagonist phentolamine into the affected area.

20.3.2 Epinephrine

20.3.2.1 Pharmacology

Epinephrine (EPI) is an endogenous catecholamine synthesized mainly in the adrenal medulla. It has a very short half-life (2–3 minutes) and is degraded by COMT and MAO.

20.3.2.2 Clinical Effects

EPI acts on the α_1-, α_2-, β_1-, and β_2-adrenoceptors in a dose-dependent fashion. As noted previously, at low infusion doses, the hormonal β_2-adrenoceptors are first affected; higher epinephrine concentrations are required to reach the innervated α_1- and β_1-receptors. Thus, at low infusion doses, the prominent action is vasodilation, especially in the skeletal muscle vascular bed, combined with an increase in heart rate and some increase in contractility mediated by β_2-adrenoceptor stimulation. These actions help redirect blood flow to the muscles to help either fight or flee a predator. Clinically, the reduced SVR is manifested by a fall in the diastolic blood pressure with an increased pulse pressure due to improved stroke volume and often an increased systolic blood pressure. As the infusion rate is increased further (>~0.1 mcg/kg/min), action at the α_1-adrenoceptor counteracts the vasodilating action and begins to dominate with a rise in both the systolic and diastolic blood pressure. Contractility and heart rate increase further due to β_1 effects with increased infusion dose. In addition, at higher infusion doses, Epi increases tone in the veins through α_1-adrenoceptor activation, which decreases their compliance and increases venous return, further supporting the increase in cardiac output. Increased cardiac output likely increases pulmonary artery pressures rather than the pressure being increased by pulmonary artery vasoconstriction. In patients with preexisting pulmonary hypertension, Epi can significantly increase PVR, but in normal patients, this is not an important hemodynamic effect. Epi also relaxes smooth muscle in the airways and GI tract and EPI has a variety of metabolic effects such as increasing ketogenesis, glycolysis, and gluconeogenesis.

20.3.2.3 Clinical Indications

Epi is the vasoactive agent of choice in cardiac arrest (0.01 mg/kg/dose IV/IO or 0.1 mg/kg/dose intratracheally) and many postarrest situations. It is also the drug of choice to treat anaphylaxis. At cardiac arrest doses, EPI dramatically increases SVR, which leads to improved coronary and cerebral perfusion pressures even though global cardiac output is reduced. High-dose epinephrine in arrest situations is not beneficial and may be harmful; therefore, it should not be routinely used.

Historically, in children with low cardiac output and hypotension seen in cardiogenic shock, hypodynamic septic shock, and postarrest situations, Epi was used as a continuous infusion (usual dosage ranges from 0.01 to 1 mcg/kg/min). Studies in adults, however, showed that NE is preferred in cardiogenic and hypodynamic septic shock. Epi may also be used in cases of anaphylaxis where a degree of myocardial dysfunction exists. In addition, Epi may benefit patients with anaphylaxis since it is a bronchodilator and inhibits mast cell degranulation. Epi in conjunction with a vasodilator such as nitroprusside may improve distal perfusion in low cardiac output and high SVR states.

Epinephrine may be used initially in the postarrest setting; however, transition to a more appropriate cardiovascular regimen such as norepinephrine with or without dobutamine is recommended.

Epinephrine acts at all adrenergic receptors; at low infusion doses, the action at the β_2-adrenoceptors is responsible for much of its hemodynamic effect.

20.3.2.4 Adverse Effects

Although EPI increases coronary perfusion due to its effects on increasing perfusion pressure at higher infusion doses, at lower infusion doses, diastolic blood pressure falls secondary to reduced systemic vascular tone by its β_2-adrenergic effect; pulse pressure increases since systolic blood pressure is also increased by its positive inotropic effect. However, increased contractility and heart rate increase MVO_2 which increases coronary blood flow. At higher infusion doses that increase SVR, Epi increases afterload. When combined with the increase in heart rate, MVO_2 is markedly increased, which is not favorable in the patient with cardiogenic shock. Its potential to cause myocardial ischemia is of importance in adults with coronary disease.

EPI increases automaticity and may be arrhythmogenic causing ventricular tachyarrhythmias. Metabolic effects of EPI (◘ Table 20.4) include hypokalemia (β_2-adrenoceptor-mediated K^+ influx into muscle cells) and hyperglycemia (increased glycolysis, gluconeogenesis, and suppressed insulin release). To support gluconeogenesis, EPI increases the release of lactate from skeletal muscle that is used by the liver for glucose synthesis (Cori cycle). Thus, an increased lactate concentration is commonly observed when using an epinephrine infusion, limiting lactate's use as a marker of tissue perfusion. Of note, when lactate rises due to Cori cycle activation, there is *no* metabolic acidosis as compared with increased lactate concentrations associated with inadequate tissue perfusion. Extravasation injury is also a potential complication.

A recent randomized controlled trial comparing NE to Epi in cardiogenic shock due to an acute MI documented a significantly higher incidence of refractory cardiogenic shock and lactic acidosis associated with Epi despite similar increases in cardiac output. The heart rate was significantly higher in the Epi group, and the trial was stopped by the safety board because of the adverse effects associated with Epi. This is consistent with the different actions of these catecholamines; endogenous Epi likely helped a species survive in a world with predators by increasing cardiac output, glucose, and blood flow to skeletal muscles. Unfortunately, these actions redirect blood flow from the splanchnic and renal circulation in sepsis models. Thus, Epi often increases global cardiac output, but renal and splanchnic perfusion and thus function may be compromised.

Epinephrine has important hemodynamic and metabolic effects that may limit its effectiveness as a vasoactive agent. Low to moderate doses tend to redirect the increased cardiac output to skeletal muscles and away from the splanchnic and renal circulations. Glucose and lactate concentrations increase, and potassium concentration falls during an Epi infusion.

Table 20.4 Noncardiovascular effects of vasoactive agents

Noncardiovascular effect	Mechanism	Receptor (agent)
Metabolic		
Increased glucose concentration	↑ Skeletal muscle and liver glycogenolysis ↑ Hepatic gluconeogenesis ↑ Glucagon release ↓ Pancreatic insulin release	β_2-adrenoceptors (Epi) β_2-adrenoceptors (Epi) β_2-adrenoceptors (Epi) α_2-adrenoceptor (Epi)
Increased lactate concentration	↑ Skeletal muscle release (Cori cycle)	β_2-adrenoceptors (Epi)
Decreased K^+ concentration	Movement into muscle cells	β_2-adrenoceptors (Epi, albuterol)
Endocrine		
↓ TRH, prolactin, LH, growth hormone	Decreased release of hormones from anterior pituitary	DA_2 receptor (dopamine)
↓ TSH	Inhibits TRH-stimulated release of TSH from thyroid	DA_2 receptor (dopamine)
↓ Renin release from juxtaglomerular cells	Indirect effect of receptor activation	DA_1 receptor (dopamine)
↑ ACTH release from pituitary gland	Acts synergistically with corticotropin releasing factor	V_{1b} receptors (vasopressin and oxytocin)
Immune, hematologic		
Transient T-cell hyporesponsiveness	Secondary to lower prolactin levels	DA_2 receptor (dopamine)
Increased PMN concentration	Demargination of PMNs	β_2-adrenoceptor (Epi)
Decreased mast cell response	Inhibit release of histamine and leukotrienes from mast cells	β_2-adrenoceptor (Epi)
Decreased endotoxin-induced release of proinflammatory mediators	Inhibition of lymphocyte, macrophage activation, mediated by increased intracellular cAMP	β_2-adrenoceptor (Epi) Milrinone
Decreased levels of circulating proinflammatory mediators		Levosimendan, vasopressin
Increased platelet aggregation response	Appears to increase platelet sensitivity to aggregating agents such as fibrin	α_2-adrenoceptor (Epi)
Increased coagulation	Vasopressin stimulates the release of von Willebrand factor	V_2 receptors

K+ potassium, *TRH* thyroid releasing hormone, *TSH* thyroid-stimulating hormone, *LH* luteinizing hormone, *PMN* polymorphonuclear leukocyte

20.3.3 Phenylephrine

20.3.3.1 Pharmacology

Phenylephrine is a selective α_1-adrenergic agonist. It is structurally similar to epinephrine, only lacking a hydroxyl group. It has a rapid onset and short duration of action (5–10 min) and can be given as a bolus (5–20 mcg/kg/dose) or continuous infusion (0.1–0.5 mcg/kg/min).

20.3.3.2 Clinical Effects

Phenylephrine causes significant arterial vasoconstriction and thus elevates SVR and PVR. It has no inotropic properties; therefore, if cardiac function is impaired, cardiac output may be reduced by the increase in afterload even though the blood pressure increases.

20.3.3.3 Clinical Indications

Phenylephrine has limited clinical uses. It may be helpful in cases of hypotension due to spinal shock or during spinal anesthesia. It may also be used to elevate SVR and promote pulmonary blood flow (by reversing shunt) in cases of hypercyanotic spells associated with tetralogy of Fallot.

20.3.3.4 Adverse Effects

Adverse effects are primarily due to decreased end-organ perfusion. Renal and splanchnic ischemia are of particular concern. Phenylephrine should be avoided in patients with pulmonary artery hypertension.

20.3.4 Dobutamine

20.3.4.1 Pharmacology

Dobutamine was developed by systematic modification of the catecholamine molecule in a search for a selective inotropic agent with limited peripheral vascular effects. Unlike other commonly infused catecholamines, dobutamine consists of two isomers having different adrenergic activity, which achieves its desired hemodynamic effect:

(+) Isomer	Strong β_1, β_2 agonist and α_1 *antagonist*
(−) Isomer	Weak β_1, β_2 agonist and α_1 *agonist*

Dobutamine has a unique pharmacologic action due to opposing actions of the two isomers on α_1 adrenoceptors resulting in mainly β-adrenoceptor stimulation. In addition, a long-lasting active metabolite has α_1 antagonist activity.

The pharmacokinetics of dobutamine are unclear with both linear and nonlinear kinetics reported. The half-life is ~2 minutes and it is metabolized by COMT. The 3-O-methyldobutamine metabolite is also a potent α-adrenergic antagonist and may add to the vasodilating action seen with dobutamine, especially if terminal renal elimination of the metabolite is impaired. The usual dosage range for a continuous infusion of dobutamine is 2.5–20 mcg/kg/min, although as with other vasoactive agents wide interindividual variation was observed in children with clearance varying over a 40-fold range.

20.3.4.2 Clinical Effects

Excess vasodilation and hypotension may be seen in some patients receiving dobutamine secondary to its intrinsic α_1-adrenoceptor blocking activity.

The net effect of the combined isomers is significant inotropy with trivial, if any, α_1-mediated vasoconstriction. Dobutamine's β_2 effects and intrinsic α-adrenergic antagonist activity counter its α_1-adrenergic vascular effects, with net vasodilation in most patients. Dobutamine's β_2 effects are thought to decrease SVR and PVR; however, endogenous sympathetic withdrawal once cardiac function is improved likely contributes to the reduction in SVR. In

addition, the intrinsic α-adrenergic antagonist activity of the (+)-isomer and metabolite contributes to reduced SVR and PVR. Dobutamine's intrinsic α-adrenergic antagonist activity suggests that it should be used cautiously in vasoplegic shock since it may further lower SVR. The combination of dobutamine and NE has been recommended in adults to selectively adjust SVR and improve cardiac contractility.

Dobutamine is less likely to produce tachycardia and arrhythmias than Epi or dopamine. Like other β-adrenergic agonists, dobutamine also improves diastolic relaxation (lusitropy). With its limited α_1 effects, dobutamine may be safer for peripheral venous administration while central access is being obtained.

20.3.4.3 Clinical Indications

Dobutamine can improve cardiac function in the failing heart. Its cardiovascular profile and short half-life make it a good initial choice for the child in congestive heart failure (e.g., myocarditis, cardiomyopathy). Transition to a phosphodiesterase inhibitor can be made later in the child's course if necessary. Dobutamine can be used in conjunction with other agents (e.g., NE or Epi) in the child with low CO and hypotension and may be useful combined with NE in children with vasoplegic septic shock. Adult studies observed that combination treatment with dobutamine and NE is superior to Epi or dopamine in patients with postarrest cardiac dysfunction.

20.3.4.4 Adverse Effects

Although dobutamine can improve myocardial performance, often without significant tachycardia, it still increases MVO_2. Ischemia with high dosing or prolonged use may rarely occur. Tachydysrhythmias are a risk, but less so than with epinephrine or dopamine. As noted above, hypotension may be worsened when used in vasoplegic shock. Dobutamine often has no metabolic side effects, but increased glucose and decreased potassium concentration may be observed.

20.3.5 Dopamine

20.3.5.1 Pharmacology

Dopamine is an intermediary compound in the production of EPI and NE. The half-life is approximately 2 minutes. Exogenous dopamine interacts with dopaminergic and adrenergic receptors in a dose-related fashion; however, the latter action is mediated largely by dopamine-stimulating NE release from sympathetic nerve terminals. Thus, dopamine is categorized as an indirect-acting catecholamine. This has clinical implications, since, as noted previously, chronically stressed patients deplete their sympathetic nerve NE stores; thus, dopamine's cardiac effects are attenuated in this setting.

Dopamine has a direct effect through dopamine receptors on renal tubules enhancing natriuresis.

Dopamine clearance appears to be age-related. In general, children under 2 years of age have a significantly greater rate of clearance and may require higher infusion rates to produce desired clinical effects, although wide interindividual variation (up to 10- to 20-fold) in clearance is observed. Concomitant administration of dobutamine causes dopamine clearance to increase linearly, perhaps due to improved renal and hepatic perfusion.

20.3.5.2 Clinical Effects

When dopamine is administered, its effects are dose-related, with the caveats regarding variation in pharmacokinetics noted previously:

Low dose (1–5 mcg/kg/min)	$DA_1 > \beta > \alpha_1$	Renal/splanchnic vasodilation, natriuresis
Intermediate dose (5–8 mcg/kg/min)	$\beta > \alpha_1 > DA_1$	Increased inotropy/chronotropy
High dose (> 10 mcg/kg/min)	$\alpha_1 > \beta > DA_1$	Increased SVR, PVR

20.3.5.3 Clinical Indications

Historically, low-dose dopamine was thought to improve renal perfusion and prevent progressive renal dysfunction. However, any improvement in renal perfusion and urine output is likely primarily due to maintaining an appropriate mean arterial pressure and cardiac output. Multiple clinical studies showed no benefit of low-dose dopamine in preventing renal dysfunction in normotensive patients. Based on the lack of clinical evidence and the potential for adverse endocrinologic and immunologic effects, infusing low-dose dopamine as a therapeutic option in the prevention or treatment of acute renal failure should be abandoned.

For children with poor cardiac function, a direct-acting vasoactive agent is preferred to an indirect-acting agent such as dopamine. A recent study randomized 120 children with fluid-refractory septic shock to dopamine or epinephrine; mortality was significantly increased in the dopamine group. In addition, healthcare-associated infections were significantly more common in the dopamine group, whereas hyperglycemia was more common in the epinephrine group. Thus, the role of dopamine in the management of shock remains limited.

There is little to no evidence to support the use of renal low-dose dopamine in children with shock; direct-acting vasoactive agents are preferred.

20.3.5.4 Adverse Effects

At high doses, α_1-adrenergic effects may cause clinically significant impairment of end-organ perfusion. Extravasation injury and dysrhythmias (especially supraventricular) may occur. There also is concern that dopamine may compromise immune function by decreasing serum prolactin concentration, therefore increasing susceptibility to infection. In addition, dopamine suppresses TSH release from the anterior pituitary gland prolonging recovery from euthyroid sick syndrome and raising the concern that dopamine may suppress thyroid function. The thyroid axis cannot be tested if the patient is on a dopamine infusion since dopamine potently suppresses TRH-stimulated TSH release. Because of these concerns, the use of dopamine as a primary cardiovascular agent is decreasing.

Dopamine has potentially important effects on endocrine function, which is a further reason to limit its use.

20.3.6 Isoproterenol

20.3.6.1 Pharmacology

Isoproterenol (ISO) is a synthetic derivative of NE where an isopropyl group is added to the N-terminal. The isopropyl addition changes the receptor affinity such that there is potent β-adrenergic activity but no α_1 activity. ISO has a half-life of ~2 minutes. The usual dosage range for ISO is 0.01–1 mcg/kg/min.

20.3.6.2 Clinical Effects

As a pure β_1 and β_2 agonist, ISO increases inotropy and chronotropy while decreasing SVR and PVR and relaxing venous tone. Due to its strong β_2 activity, ISO also causes bronchodilation, and it antagonizes hypoxic pulmonary vasoconstriction, which can increase intrapulmonary shunt.

By increasing both heart rate and contractility, ISO increases MVO_2, but its potent effects on SVR may decrease coronary diastolic blood flow due to lowering diastolic blood pressure; marked tachycardia further adds to the risk of myocardial ischemia by decreasing the time for diastolic coronary blood flow. Therefore, ISO should be avoided in children with specific heart conditions (see below).

20.3.6.3 Clinical Indications

With its potential to cause myocardial ischemia and the advent of newer vasoactive agents, ISO has limited clinical utility. It is most often used in cases of refractory bradycardia (especially in the transplanted heart). It may be useful in severe asthma when no underlying heart disease exists, although selective β_2-adrenergic agonists are preferred.

20.3.6.4 Adverse Effects

Isoproterenol is a potent β-adrenoceptor agonist, but its potent vasodilating effects and marked tachycardia increase the risk of myocardial ischemia. It is mainly indicated in patients with refractory bradycardia. Isoproterenol should be avoided in children with left ventricular outflow tract obstruction, shunt lesions with low diastolic blood pressure, ischemic heart disease, and arrhythmias.

ISO is contraindicated in children with obstruction of the left ventricular outflow tract (e.g., subaortic stenosis, hypertrophic cardiomyopathy), as it increases the outflow pressure gradient. It also should be avoided in children with lesions associated with low diastolic pressures (e.g., systemic-pulmonary shunts and aortic regurgitation), as it will further decrease diastolic pressure and coronary filling. ISO is contraindicated in any child with ischemic heart disease and it may cause tachydysrhythmias. Although ISO is a potent bronchodilator, its nonselective β-adrenergic effects results in excessive tachycardia compared with β_2-adrenoceptor selective agents; thus, myocardial ischemia has occurred in children with status asthmaticus treated with ISO. Finally, like other potent β_2-adrenergic agonists, ISO causes potassium to move into cells, reducing the plasma concentration and perhaps increasing the risk for arrhythmias, especially in the patient who is already hypokalemic.

20.3.7 Vasopressin

20.3.7.1 Pharmacology

Arginine vasopressin is produced in the paraventricular nucleus of the hypothalamus and transported via neuronal axons to the posterior pituitary for secretion. Also known as antidiuretic hormone (ADH), vasopressin is released in response to hemodynamic, osmotic, and nonosmotic stimuli.

When the peripheral and central osmoreceptors sense an increased plasma osmolality, vasopressin is released from the posterior pituitary. Multiple nonosmotic stimuli such as pain, nausea, hypercarbia, hypoxia, and stress associated with catecholamine release all can stimulate vasopressin release. This may result in excessive free water conservation and the syndrome of inappropriate ADH release. Decreased effective circulating volume is a potent stimulus for the *appropriate* release of ADH. During hypovolemia, baroreceptors and stretch receptors located in the left atrium, aortic arch, and carotid sinus respond to reduced pressure and volume by stimulating the release of vasopressin from the posterior pituitary.

Vasopressin has multiple hemodynamic effects including V_1 receptor-mediated vascular smooth muscle contraction and endothelial NO-mediated selective vasodilation of the cerebral and pulmonary circulations.

Vasopressin has multiple physiologic effects dependent upon specific receptor interaction. Three G-protein-coupled vasopressin receptors, termed V_{1a}, V_{1b}, and V_2, have been characterized. V_{1a} receptors are widely distributed and occur mainly on vascular smooth muscle; receptor binding activates the phospholipase C-phosphatidylinositol pathway increasing cytosolic Ca^{++} that mediates vascular smooth muscle contraction. Vasopressin may also restore vascular tone by blocking potassium-sensitive adenosine triphosphate (K^+-ATP) channels; inhibition of these channels increases Ca^{++} entry into the cytosol, ultimately causing vasoconstriction. Vasodilation of cerebral and

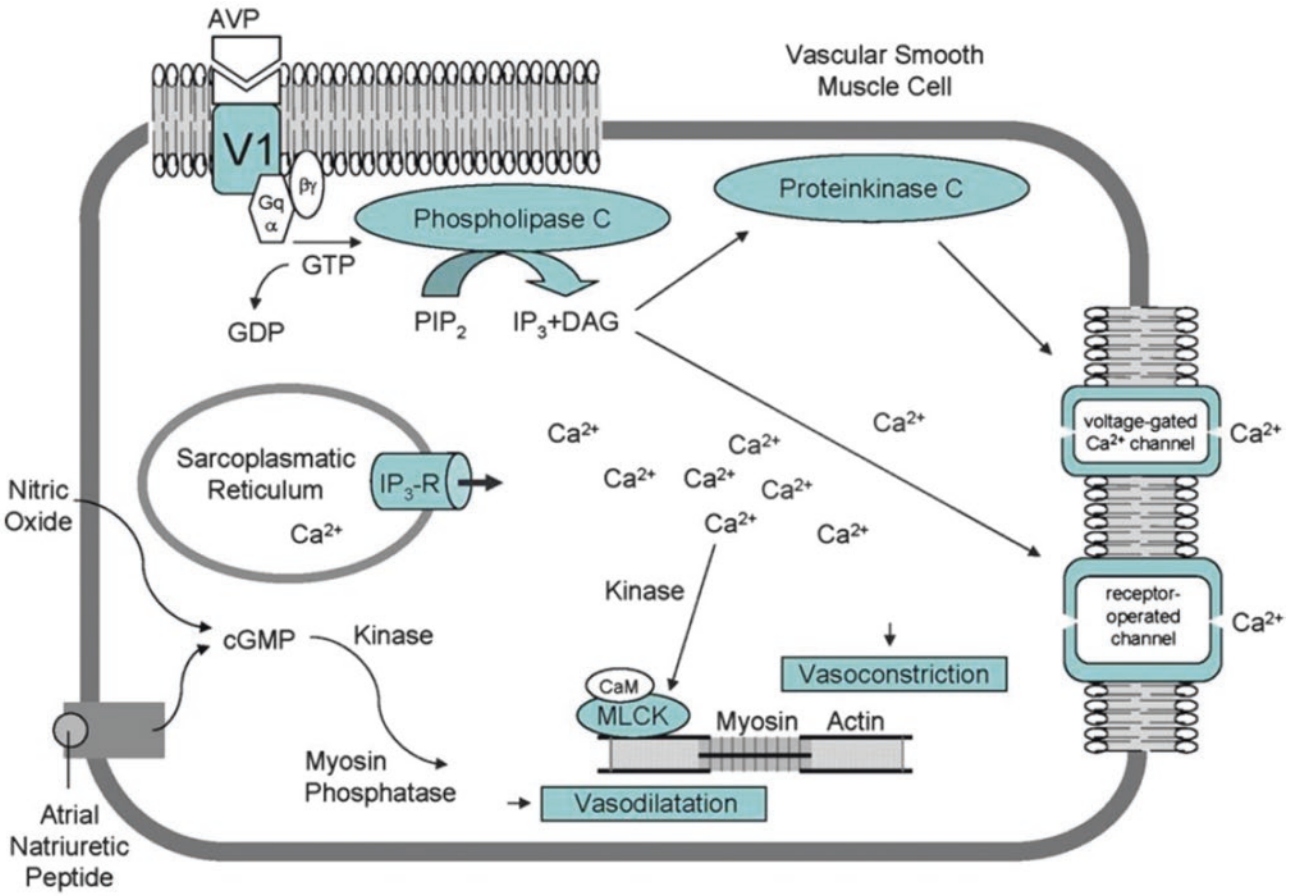

Fig. 20.8 Signal transduction of vasopressin (VP) analogues on V1 receptor (V1R) in vascular smooth muscle cells. Abbreviations: CaM, calcium-calmodulin complex; GDP, guanosyl diphosphate; Gq α, β, γ, G-protein subunits; GTP, guanosine triphosphate; MLCK, myosin light-chain kinase; black arrows, activation of pathways. (Figure used with express permission from Maybauer MO, Maybauer DM, Enkhbaatar P, Traber DL. Physiology of the vasopressin receptors. Best Practice and Research Clinical Anesthesiology. 2008;22(2):253–263)

pulmonary circulations by a low-dose vasopressin infusion is likely secondary to the induction of endothelial nitric oxide (Fig. 20.8).

V_{1b} receptors are expressed in the anterior pituitary; receptor stimulation increases adrenocorticotrophic hormone (ACTH) and endorphin release. V_2 receptors are expressed predominantly in the renal collecting duct system; vasopressin receptor binding mediates an antidiuretic effect in the renal collecting ducts conserving free water during hypertonic and/or hypovolemic states. Vasopressin also acts at oxytocin and purinergic receptors, which stimulate endothelial nitric oxide production. In the pulmonary vascular bed, vasopressin action at oxytocin receptors reduces PVR; thus, vasopressin may be useful in a deteriorating patient with severe pulmonary hypertension by increasing SVR and coronary perfusion pressure while not worsening PVR.

Whereas concentrations of ADH necessary to regulate water reabsorption are extremely low (1–7 pg/mL), higher concentrations are needed to produce vasoconstriction (10–200 pg/mL). Despite high levels of ADH during states of decreased effective circulating volume, osmoregulation often is kept intact. This is due to alterations in the relationship between plasma osmolality and vasopressin such that higher vasopressin levels are required to maintain normal osmolality in the setting of hypovolemia.

The half-life of vasopressin is 6–20 min. It is metabolized by a variety of peptidases in the liver and kidney. The usual dosage range used for hemody-

namic effects is 0.00017–0.008 U/kg/min (equivalent to 0.17 mU/kg/min–8 mU/kg/min). Studies in adults have used doses of 0.04–0.06 U/min to produce peripheral vasoconstriction. Terlipressin (tricyl-lysine-vasopressin, not FDA-approved) is a synthetic prodrug form of vasopressin that has comparable pharmacodynamics; vasopressin is slowly released by enzymatic action on the prodrug. The half-life of terlipressin is ~6 h, and its duration of action is 2–10 h, as opposed to the short half-life and duration of action (30–60 min) of vasopressin.

20.3.7.2 Clinical Effects

Vasopressin has important vasoconstrictor activity during states of hypotension due to excessive vasodilation. Vasopressin levels are acutely elevated during hemorrhagic and septic shock. However, if hemodynamic instability continues (particularly in cases of vasodilatory septic shock), vasopressin levels fall dramatically. Decreased vasopressin levels may be secondary to depletion of pituitary stores and due to nitric oxide inhibition of vasopressin release.

Vasopressin potentiates the vasoconstrictor effects of catecholamines and in septic shock can reduce the need for NE to support the blood pressure; however, these effects are diminished or absent in certain regional circulations; specifically, the cerebral, coronary, and pulmonary circulations are not as sensitive to vasopressin-induced vasoconstriction. As noted previously, these regional effects are likely due to V_1 and oxytocin receptor-mediated release of endothelial-derived nitric oxide in those vascular beds. Vasopressin selectively constricts the glomerular efferent arteriole raising glomerular filtration pressure; clinical studies in septic patients show improved creatinine compared with NE use. In a large randomized trial (VASST trial) of vasopressin + NE vs. NE alone in septic shock, patients with less severe renal injury had improved survival with the combination therapy. One limitation of this study is that fixed doses of both drugs were used, ignoring the likely variation in pharmacokinetics and pharmacodynamics discussed above.

Vasopressin may have negative inotropic effects mediated by NO. In normal subjects, it decreases cardiac output by stimulating the baroreflex (increased SVR and blood pressure causing reflexive bradycardia).

In patients hypotensive due to vasoplegia, vasopressin administration does not produce an antidiuretic effect; instead, urine output often increases, which is thought to be secondary to improved hemodynamics and glomerular filtration pressure.

20.3.7.3 Clinical Indications

The clinical pharmacology of vasopressin suggests it may be of value in refractory vasodilatory shock. Its action is not dependent on the adrenergic system and thus may be used in settings where NE or Epi are not effective. However, adult and limited pediatric data failed to demonstrate improved outcomes when using low-dose vasopressin versus norepinephrine in septic shock. A multicenter randomized controlled trial of low-dose vasopressin in vasodilated pediatric shock observed a worrisome, but not significant, increase in overall mortality (69 total patients, 30% mortality in vasopressin arm vs. 15% mortality in placebo arm). A meta-analysis supports the use of vasopressin or terlipressin for renal insufficiency in hepatorenal syndrome.

During adult CPR, vasopressin alone or combined with epinephrine had no beneficial effects on outcome. Therefore, the 2015 American Heart Association treatment recommendations for cardiac arrest removed vasopressin from the ACLS guidelines for out-of-hospital cardiac arrest. However, based on the results from two randomized controlled trials, vasopressin combined with corticosteroids (methylprednisolone) and epinephrine may be con-

sidered for in-hospital adult arrests. Due to the lack of any trial data, vasopressin has no current role during pediatric CPR.

Unlike other vasoconstricting agents, animal studies and limited clinical data show that vasopressin can reduce pulmonary vascular tone, especially if it is increased at baseline. Studies in isolated human pulmonary arteries did not show that vasopressin induced vasoconstriction. Several case series reported that unlike other vasopressors, vasopressin may be helpful in the management of refractory pulmonary hypertensive crisis by increasing SVR to improve coronary perfusion pressure while not worsening and indeed potentially reducing PVR. Similarly, in patients with chronic hepatic dysfunction, pulmonary hypertension may develop. Case reports suggest that vasopressin/terlipressin may have favorable effects in this setting by increasing SVR while improving PVR.

20.3.7.4 Adverse Effects

Adverse effects are mainly secondary to its vasoconstrictor effects. Though vasoconstriction is less pronounced in the coronary circulation, myocardial ischemia can occur especially with underlying heart disease.

Unlike all other vasoconstricting agents, vasopressin may reduce PVR through stimulation of NO release mediated by action at pulmonary endothelial oxytocin receptors. Thus, it may be useful in unstable patients with pulmonary hypertension and in patients with portopulmonary hypertension. Since it acts through a non-adrenergic mechanism, vasopressin may be useful in vasoplegic shock that is adrenergic-unresponsive.

20.4 Vasodilators for Circulatory Support

20.4.1 Physiologic Effects

There are several common misconceptions regarding the action of vasodilators when used to support the circulatory system. For example, publications often state that vasodilators are used to improve cardiac output and reduce venous return, but this statement is physiologically impossible since at steady state cardiac output must equal venous return. The misperception results from the effect of vasodilators on venous and atrial compliance; a decrease in CVP or left atrial/pulmonary wedge pressure (LAP/PWP) is perceived to represent a decline in venous return. Instead, by reducing tone in the venous capacitance system, where ~70% of blood volume is normally located (see ▶ Chap. 15, Regional Circulation), venous compliance is increased so that a given volume in the atria is associated with a lower filling pressure (◘ Fig. 20.9).

As seen in ◘ Fig. 20.9, vasodilators shift the ventricular pressure-volume curve (i.e., compliance). If the patient receives fluid to increase the venous filling pressure back toward the previous level, preload (i.e., end-diastolic volume) is increased since a higher volume is now in the heart at a lower pressure.

At steady state, cardiac output must equal venous return. Thus, vasodilator-induced improvement in cardiac output is associated with a concomitant increase in venous return as the increased venous compliance allows a higher volume in the venous system at a lower filling pressure.

Vasodilators are also assumed to routinely decrease blood pressure secondary to the reduction in SVR. If the patient has inadequate intravascular volume, blood pressure will fall, but in patients with poor cardiac function, regulatory mechanism such as increased SNS activity, renin-angiotensin-aldosterone activation and increased vasopressin release all increase peripheral vascular resistance to maintain perfusion pressure as stroke volume (SV) falls. As seen in ◘ Fig. 20.10, a series of curves illustrate the relationship between SVR and SV; as cardiac pumping function declines, stroke volume declines as SVR rises. Recall that cardiac output (CO) = (MAP – CVP)/SVR, where MAP is mean arterial pressure and CVP is central venous pressure. If HR is kept constant, then SV ∝ (MAP – CVP)/SVR. In a patient with normal contractility, as seen in the top curve, increasing SVR from point A to B has little effect on SV; instead, the blood pressure increases. This relationship continues until the increased afterload reaches a point where the ventricle is no longer able to overcome the vascular resistance and then SV begins to fall.

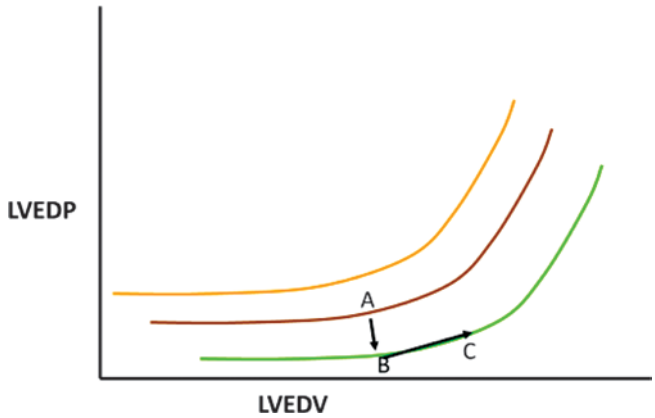

Fig. 20.9 Left ventricular compliance curves are illustrated, where LVEDP is left ventricular end-diastolic pressure and LVEDV is left ventricular end-diastolic volume. The middle curve illustrates a patient with increased LVEDP and moderate ventricular filling. Adding a vasodilator shifts the curve down so that a slightly higher LVEDV (point B) is associated with a lower LVEDP illustrating that filling pressures often do not reflect the end-diastolic volume. If fluid is given after the vasodilator to increase filling pressure, note at point C that a much higher preload is achieved without raising the LVEDP to the same extent as seen before the vasodilator was added (point A). Factors that may shift the curve up and to the left (orange curve) include right ventricular volume overload, increased PEEP, and adding a vasoconstrictor that increases afterload and reduces ventricular emptying

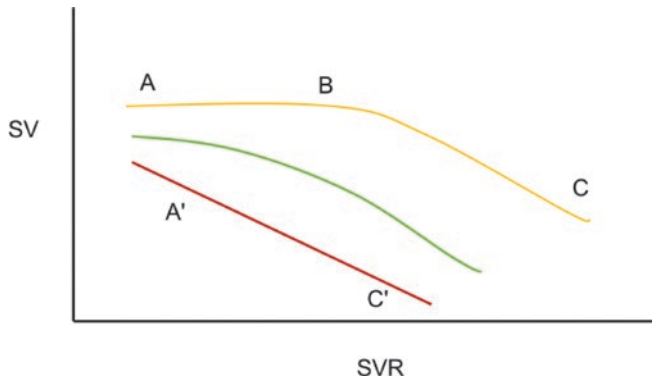

Fig. 20.10 Relationship between stroke volume (SV) and SVR in patients with different degrees of ventricular pumping function. The top curve illustrates a normal ventricle. The middle curve illustrates a patient with worsening pump function. The bottom curve illustrates a patient with severe ventricular dysfunction. As explained in the text, in the normal ventricle as SVR is increased from point A to B, SV is maintained so that blood pressure must increase. In the bottom curve as SVR increases, SV falls proportionally resulting in little change in systemic pressure

In a child with poor cardiac contractility, as illustrated by the bottom curve in Fig. 20.10, the SV declines linearly as SVR increases; the driving pressure (MAP – CVP) changes very little as you move along the curve from A′ to C′. This illustrates a significant limitation of assuming that an increase in MAP reliably reflects an improvement in cardiac output in a patient with poor pump function. Indeed, in the patient whose endogenous systems have increased their SVR, using a vasodilator to reduce SVR from C′ to A′ often improves SV with little change in blood pressure!

Furthermore, unlike vasoactive agents that improve cardiac output by adrenergic stimulation, vasodilators often improve cardiac output while reducing myocardial oxygen demand. Adrenergic agonists increase myocardial oxygen demand by increasing both heart rate and contractility. If the vasoactive

agent also increases SVR, myocardial wall stress is increased, which further increases myocardial oxygen demand. In contrast, if cardiac output improves in response to a vasodilator, the patient's endogenous catecholamine stress response is reduced, with further beneficial effects on myocardial energetics.

Myocardial oxygen demand (MVO_2) is determined by the heart rate and ventricular stroke work; the latter is determined by the volume pumped times the pressure generated to perform that volume work. The left ventricular stroke work index (LVSWI) = (MAP – LAP) * SVI * 0.0144 dyne-sec-cm^{-5}; SVI is stroke volume index (ml per beat/m^2). For a given LVSWI, volume work requires less oxygen demand than pressure work. You can appreciate this difference by using your respiratory muscles to exhale while your lips are tightly pursed. This clearly requires more effort and energy than exhaling a large volume of air with your mouth wide open. The same is true for the heart, which is much happier doing volume rather than pressure work. Thus, when the heart muscle is weak, reducing resistance reduces the effort to move the stroke volume into the arterial circulation and has the added advantage of reducing myocardial oxygen demand while cardiac output is increased.

Volume work requires less energy than pressure work, so vasodilators increase cardiac output while decreasing myocardial oxygen demand.

In summary, vasodilators have the following effects when used to support the failing circulation, such as seen following cardiopulmonary bypass (CPB), which is typically associated with increased SVR:

- Vasodilators increase cardiac output while reducing MVO_2.
- Blood pressure changes are a poor indicator of a change in CO; blood pressure will fall with vasodilator use if the intravascular volume is depleted. In patients with adequate intravascular volume, reducing SVR increases pulse pressure as recognized by a fall in the diastolic blood pressure; an improved SV also may increase the systolic BP so that the effect on pulse pressure is further augmented.
- In patients with poor cardiac function, heart rate may decline with vasodilators as an indirect indicator of reduced endogenous SNS stimulation in response to an improved cardiac output.
- Vasodilators typically reduce tone in the venous capacitance system; this increases diastolic compliance so that a fall in filling pressure does *not* reliably indicate a fall in venous return.
- If a vasodilator improves cardiac output, then venous return increases even though filling pressure often falls as noted above.
- Restoring filling pressure after adding a vasodilator reliably increases preload.
- Infants with functional univentricular hearts and systemic-to-pulmonary artery shunts often have excessive pulmonary blood flow that is exacerbated if SVR is increased. Thus, in this setting, systemic vasodilators can improve systemic perfusion and reduce pulmonary overcirculation.
- Vasodilators should *not* be used in patients with low cardiac output due to a fixed obstruction that limits cardiac output.

20.5 Specific Vasodilators

20.5.1 Milrinone

20.5.1.1 Pharmacology

Milrinone is a bipyridine phosphodiesterase (PDE) III inhibitor; inhibition of PDE III reduces cAMP breakdown and thus increases cytosolic cAMP concentrations in vascular smooth muscle and cardiac cells. Since cAMP is the

secondary messenger for β-adrenergic agonists, the cellular effects are like those produced by β agonists: increased cardiac contractility, lusitropy, and chronotropy combined with systemic and venous vasodilation.

Milrinone has a half-life of approximately 2–3 hours and is ~70% protein-bound. It is mainly excreted unchanged by the kidney and therefore requires dose adjustment in renal insufficiency. A small percentage is hepatically metabolized. Usual dosages include a loading dose of 50 mcg/kg (may be omitted due to the risk of hypotension) and a continuous infusion range of 0.1–1 mcg/kg/min. Sometimes the loading dose is divided into five 10 mcg/kg boluses with fluid given after a mini-bolus if there is evidence for a vasodilation-induced fall in blood pressure.

20.5.1.2 Clinical Effects

Vasodilation occurs in both the systemic and pulmonary vascular beds, reducing both SVR and PVR. In addition, milrinone relaxes tone in the capacitance venous system, which helps reduce end-diastolic filling pressure. If intravascular volume is adequate, milrinone increases cardiac output and venous return (i.e., preload) in children with myocardial dysfunction, illustrating the limitation of following filling pressures as an indicator of preload in this clinical setting. MAP is usually maintained due to improved contractility and lower SVR which increase stroke volume, but if intravascular volume is low, milrinone causes hypotension from both systemic vasodilation and pooling of blood in the capacitance venous system, which reduces venous return.

Although tachycardia may be expected, milrinone usually does not significantly elevate heart rate, perhaps secondary to reduced endogenous SNS stimulation as cardiac output improves.

Milrinone can increase both the beneficial and adverse effects of β-adrenoceptor agonists by augmenting the increase in intracellular cAMP.

Since milrinone inhibits the degradation of cAMP and adrenergic agonists increase cAMP production, the combination of milrinone with a β-adrenoceptor agonist may increase both the beneficial and adverse effects on the heart and vascular systems. Like other phosphodiesterase inhibitors, milrinone has some anti-inflammatory effects.

20.5.1.3 Clinical Indications

Milrinone is an excellent choice for children with primary myocardial dysfunction (e.g., cardiomyopathy or postoperative myocardial dysfunction). Its favorable cardiovascular profile has led to its increased use in the PICU. However, due to its relatively long half-life, it should be instituted only after careful delineation of myocardial function and volume status. Based on results from a multicenter clinical trial, it is commonly used in infants and children at risk of low cardiac output syndrome after cardiopulmonary bypass.

Although milrinone is given as a continuous infusion, it is important to recognize that changes in the infusion rate will not reach a new steady-state concentration for 6 to 9 hours (i.e., about three times the half-life to reach 90% of the steady-state concentration). Therefore, if a higher concentration is desired more rapidly, a small bolus (e.g., 5–10 mcg/kg) can be given along with an increase in the infusion rate. Similarly, if excess milrinone-induced vasodilation occurs, it will take many hours for the concentration to fall after reducing the infusion rate.

20.5.1.4 Adverse Effects

Rapid infusion of the loading dose can produce hypotension. Similarly, hypotension may occur from excessive systemic and venous dilation hours after starting an infusion in a patient with impaired renal function due to the slow

accumulation of milrinone. Supraventricular and ventricular arrhythmias have been reported. Thrombocytopenia is far less common than was previously reported with amrinone.

Milrinone is a useful vasoactive agent providing afterload reduction, reduced preload pressure, and improved contractility, but its long half-life may lead to slow accumulation, especially if renal function is impaired.

20.5.2 Sodium Nitroprusside

20.5.2.1 Pharmacology

Nitroprusside acts as an NO donor to produce relaxation of both venous and arterial smooth muscles. NO stimulates guanylate cyclase in vascular smooth muscle to increase intracellular cGMP. This in turn increases cGMP-dependent protein kinase activity, which ultimately decreases Ca^{2+} influx into smooth muscle cells resulting in vasodilation.

Nitroprusside has a very rapid onset of action (less than 30 seconds) and a half-life of ~2 minutes. Its effects dissipate within 2 to 3 minutes of discontinuation. Usual dosage range for nitroprusside is 0.1–6 mcg/kg/minute.

Metabolism of nitroprusside to certain by-products may lead to toxicity. Upon contact with hemoglobin, nitroprusside rapidly forms cyanide and methemoglobin. Cyanide is slowly released into the plasma and is converted to thiocyanate by the hepatic enzyme rhodanase. Thiosulfate and vitamin B_{12} (cyanocobalamin) are important cofactors in this reaction. Thiocyanate subsequently undergoes renal excretion with a half-life of 3 days that may be increased to 9 days with renal impairment.

Unlike adrenergic agents, milrinone does not result in rapid hemodynamic effects with changes in the infusion rate (i.e., within minutes). Infusion rate changes will not reach a new steady-state concentration for 6 to 9 hours (i.e., about three times the half-life to reach 90% of the steady-state concentration). Therefore, if a higher concentration is desired, a small bolus (e.g., 5–10 mcg/kg) can be given along with an increase in the infusion rate.

Unlike nitroglycerin, nitroprusside infusion does not result in resistance or tachyphylaxis to its pharmacologic action.

20.5.2.2 Clinical Effects

Nitroprusside effectively lowers SVR and PVR; venodilation increases compliance, which decreases the filling pressures. Improved ventricular emptying secondary to afterload reduction and improved venous compliance typically reduces ventricular end-diastolic pressure (EDP), which may also reduce end-diastolic volume (EDV). The combination of reduced EDP and EDV reduces ventricular wall stress and therefore MVO_2.

Nitroprusside has no direct inotropic activity. Its effect on cardiac output is variable and depends on the presence or absence of cardiovascular pathology and the intravascular volume status. In healthy hearts with normal intravascular volume, venodilation causes blood to pool in the venous capacitance system, which reduces venous return and thus CO. In patients with left ventricular dysfunction and typically increased intravascular volume and pressure, the reduction in afterload improves ventricular ejection and thus increases CO. If there is excessive vasodilation that reduces systemic pressure, reflex activation of the SNS may increase the heart rate.

When used to control blood pressure, such as following coarctation repair, the drug-induced reduction in SVR may be counterbalanced by increased activation of the SNS. In this setting, combining nitroprusside with a β-blocker such as esmolol is often useful to achieve blood pressure control and limit reflex tachycardia.

20.5.2.3 Clinical Indications

The rapid onset and short half-life of nitroprusside helps to rapidly assess a patient's response to afterload reduction, especially when pumping function is poor and filling pressures are elevated. Its short duration of action also makes it an effective agent in the treatment of hypertensive emergencies by allowing for gradual and controlled reduction of dangerous elevations in blood pressure.

The rapid onset and short half-life of nitroprusside helps to rapidly assess a patient's response to afterload reduction, especially when pumping function is poor and filling pressures are elevated.

Its short duration of action also makes it a very effective agent in the treatment of hypertensive emergencies and for afterload reduction following certain cardiac surgeries.

When used for afterload reduction, nitroprusside is often infused in combination with an inotrope in the setting of acute myocardial dysfunction such as seen in postoperative cardiac surgery and dilated cardiomyopathy, although a similar effect may be achieved with milrinone.

20.5.2.4 Adverse Effects

Nitroprusside adverse effects are usually related to excessive vasodilation and venodilation with resultant hypotension; therefore, its use requires continuous monitoring of arterial pressure. Nitroprusside can cause progressive hypoxemia in patients with parenchymal pulmonary disease by uncoupling hypoxic pulmonary vasoconstriction, thereby increasing intrapulmonary shunting. It should be use with caution and close monitoring in patients with elevated intracranial pressure (ICP) since it may cause cerebral vasodilation leading to increased cerebral blood volume and ultimately increased ICP. Additionally, administration in patients with elevated ICP may reduce cerebral perfusion pressure if blood pressure falls resulting in cerebral ischemia. Like other systemic vasodilators, nitroprusside is contraindicated in patients with conditions that obstruct ventricular emptying such as aortic or pulmonary stenosis.

Less commonly, toxicity may result from the accumulation of metabolic by-products (see ► Boxes 20.1 and 20.2). These toxicities are more often seen in patients with hepatic (cyanide) or renal (thiocyanate) insufficiency. Serial acid-base and methemoglobin determinations should be obtained on all patients on high-dose and/or prolonged infusions.

Box 20.1 Overview of Cyanide Toxicity

- Hepatic insufficiency is a significant risk factor
- Usually seen in children with prolonged high-dose infusions (>3 days at ≥4 mcg/kg/min)
- Toxicity is due to mitochondrial poisoning by inhibiting cytochrome oxidase and oxidative phosphorylation

Signs/symptoms:

- Giddiness, confusion, headache, coma, seizures
- Metabolic acidosis
- Increased central or mixed venous O_2 saturation due to disruption of oxidative phosphorylation

Treatment:

- Discontinuation
- Increase rhodanase activity by providing thiosulfate and hydroxocobalamin
- Induce conversion to methemoglobin with amyl nitrite inhalation followed by IV sodium nitrite. Methemoglobin (MtHgb) preferentially binds cyanide and thus induces cyanide release from mitochondrial cytochrome oxidase
- Methylene blue should *not* be used to decrease MtHgb levels, as it will liberate large amounts of cyanide from the cyanomethemoglobin complex; exchange transfusion is the preferred treatment for significant methemoglobinemia caused by cyanide toxicity

Box 20.2 Overview of Thiocyanate Toxicity

- Renal insufficiency is the risk factor
- Usually seen in children with prolonged high-dose infusions (>3 days at ≥4 mcg/kg/min)

Signs/symptoms:
- Abdominal pain, nausea
- Tinnitus
- Blurred vision
- Psychosis, confusion, hyperreflexia, seizures

Treatment:
- Thiocyanate is 100 times less toxic than cyanide and generally only requires discontinuation of nitroprusside and supportive care
- Dialysis may be considered in severe cases

20.5.3 Nitroglycerine (NTG)

20.5.3.1 Pharmacology

NTG (glycerol trinitrate) is one of several organic nitrates that are metabolized within vascular smooth muscle cells to release NO, which activates the soluble form of guanylyl cyclase increasing intracellular cGMP. Besides its effects on vascular smooth muscle, NO-mediated cGMP inhibits platelet aggregation and relaxes smooth muscle in the bronchi and GI tract. Despite more than 140 years since its introduction, the precise mechanisms of NO release from NTG are still not clear; a nonenzymatic interaction with cysteine groups is one mechanism that releases NO.

The onset of action is within 1–2 minutes. The duration of action after the infusion is stopped is 2–5 minutes with an elimination half-life of 1–3 minutes.

A major limitation of long-term NTG use is the development of tolerance, which attenuates its effects. The onset and magnitude of tolerance is related to the duration and dose used. Tolerance appears to represent a reduced capacity of vascular smooth muscle to convert NTG to NO, although other mechanisms may play a role, such as increased endogenous SNS activity and/or depletion of intracellular sufhydryl groups. To limit tolerance, infusions are often used for <24 hours. If used topically, therapy is often interrupted for 8–12 hours per day.

20.5.3.2 Clinical Effects

For reasons that are not understood, NTG dilates large blood vessels (>200 μm diameter) more potently than smaller vessels, explaining why low doses of NTG preferentially dilate veins and conductance arteries and has little effect on medium and small arterioles, which are the main source of systemic vascular resistance. Thus, NTG's main action is to increase venous compliance; filling pressures (CVP and LAP) decrease, and EDV may also decrease. Heart rate may be unchanged or may increase secondary to SNS activation if cardiac output declines. The latter typically results from reduced venous return secondary to pooling in the capacitance venous system if intravascular volume is low or venodilation is excessive. SVR declines modestly; a greater decrease in PVR may be seen, especially if PVR is increased in association with an increased LAP.

NTG has a short-half life and produces relatively selective dilation of large blood vessels, especially in the venous circulation. This reduces end-diastolic pressure and may reduce end-diastolic volume if intravascular volume is low or if there is excessive venorelaxation.

Tolerance develops with prolonged infusions (>24 hours), limiting the use of NTG for long-term management.

20.5.3.3 Clinical Indications

NTG may be used to reduce high filling pressures in patients with reduced ventricular pumping function. Although NTG can dilate coronary vessels, studies during cardiac catheterization show that direct injection does not resolve angina; instead the beneficial effects are related to NTG's action on

venous pressures, which reduces ventricular wall stress and thus MVO_2. This is especially helpful in improving subendocardial perfusion. If there is coronary vasospasm, NTG's effect on the coronary vessels may be important. NTG may be helpful to more selectively reduce elevated PVR since a relatively higher proportion of resistance is on the venous side in the pulmonary circulation compared with the systemic circulation.

When used, infusions are typically started at 0.5 mcg/kg/min and titrated to the desired effect with upper infusion dose of ~5 mcg/kg/min.

20.5.3.4 Adverse Effects

Excessive venodilation may pool blood in the capacitance venous system leading to a fall in venous return and thus cardiac output and blood pressure. Facial flushing and vasodilation of meningeal arteries may occur with the latter causing headache. High doses or inadvertent bolus administration may cause profound hypotension and bradycardia secondary to high myocardial NO concentrations. A major potentially lethal side effect results from NTG's interaction with PDE type V inhibitors (e.g., sildenafil), which can markedly increase intracellular cGMP concentrations leading to profound vasodilation and life-threatening hypotension.

20.5.4 Phentolamine and Phenoxybenzamine

20.5.4.1 Pharmacology

Both phentolamine and phenoxybenzamine are nonselective inhibitors of α-adrenoceptors with no effect at β-adrenoceptors. The onset of action following phentolamine administration is 1–2 minutes with a half-life of ~19 minutes. Phenoxybenzamine has unique pharmacology since it covalently binds to the receptor, producing complete inhibition until new α-adrenoceptors are synthesized and expressed on the cell surface.

20.5.4.2 Clinical Effects

Rapid reduction in SVR along with reduced venous tone results in reduced blood pressure. Cardiac output may be maintained if intravascular volume is adequate; if ventricular pumping function is impaired, CO often improves, in part due to reflex sympathetic tachycardia. Normally, PVR is not affected by increased SNS activity unless there is increased muscularization of the pulmonary vasculature (see ► Chap. 15, Regional Circulation), so phentolamine tends to reduce SVR more than PVR.

20.5.4.3 Clinical Indications

Both agents have been used as part of a strategy to lower SVR in the perioperative management of infants following stage I palliation of hypoplastic left heart syndrome. The objective is to improve systemic blood flow, which can be monitored by a reduced oxygen saturation difference between central venous and arterial oxygen saturation.

Phenoxybenzamine is also used in the management of children with pheochromocytoma to limit the risk of severe hypertension.

20.5.4.4 Adverse Effects

Hypotension and reflex tachycardia are the major adverse effects. Clinicians should be prepared to manage excessive vasodilation with volume administration.

20.6 Novel Agents

20.6.1 Levosimendan

20.6.1.1 Pharmacology

Levosimendan is a calcium-sensitizing agent that produces inodilator effects. Its mechanisms of action include calcium sensitization of contractile proteins in the myocardium and the opening of ATP-dependent potassium channels in vascular smooth muscle. The latter action leads to hyperpolarization and reduced calcium entry into the smooth muscle cell, resulting in vasodilation. These vasodilatory effects are seen throughout vascular beds, including the coronary, pulmonary, and cerebral circulations as well as the capacitance venous system. The latter leads to increased venous compliance and reduced end-diastolic pressure.

Although levosimendan is also an inhibitor of PDE III, this action, at low doses, does not contribute to its clinical effects. Levosimendan increases myofilament calcium sensitivity by binding to cardiac troponin C in a calcium-dependent manner. This stabilizes the calcium-induced conformational change of troponin C, thereby sensitizing the cardiac myofilaments to calcium. Since levosimendan increases contractility without increasing intracellular Ca^{++} concentration, there is less cellular work and associated oxygen consumption related to the transport of increased cytoplasmic Ca^{++} back into the sarcoplasmic reticulum compared with adrenergic inotropic agents.

Levosimendan is extensively protein-bound. Although it is administered intravenously, it is excreted into the small intestine and reduced by intestinal bacteria to an amino phenolpyridazinone metabolite (OR-1855) which is further hepatically metabolized to an N-acetylated metabolite (OR-1896); this final metabolite is active and has a far longer half-life than the parent drug (70–80 hours vs. ~1 hour). This likely explains the prolonged hemodynamic effects seen after discontinuation of an infusion, but also is undesirable since, if hypotension develops secondary to drug effect, it is not readily reversed. Doses should be adjusted in patients with severe renal or hepatic insufficiency.

20.6.1.2 Clinical Effects

Levosimendan increases cardiac output with little effect on MVO_2. Vasodilation results in decreased systemic and pulmonary afterload, reduced LAP and RAP, and improved coronary perfusion. Although not a direct chronotrope, levosimendan may increase heart rate by vasodilation-induced activation of baroreceptor reflexes.

20.6.1.3 Clinical Indications

Levosimendan was shown to improve cardiac function and hemodynamic performance in adults with severe heart failure; however, several recent trials in medical and surgical patients with cardiac dysfunction failed to show a benefit over conventional therapy. The effects of levosimendan in children with myocardial dysfunction (both congenital and acquired) have not been fully investigated, but small studies to date appear promising, with initial studies showing improved cardiac output, appropriate heart rate, and an encouraging safety profile. However, a recent double-blind, randomized clinical trial assessing levosimendan in adults with sepsis found that treatment with levosimendan did not decrease severity of organ dysfunction or mortality and increased the likelihood of arrhythmias. Thus, larger and more rigorous studies in pediatrics are required to further elucidate the efficacy and safety of levosimendan therapy in

pediatrics. A meta-analysis of 40 clinical trials of perioperative levosimendan in adults found a higher risk of hypotension and arrhythmias when including just the five trials with low risk of bias; when including all trials, there was a mortality benefit associated with the use of levosimendan, but the quality of data was judged to be low, so no conclusions could be drawn. A recent review suggests that levosimendan may be specifically useful in patients with heart failure on β-adrenergic blockers since its action bypasses the adrenergic receptor system.

At this time, the drug is not FDA-approved, but it is approved for use in adults in ~60 countries and is currently undergoing study in the treatment of pulmonary artery hypertension.

20.6.1.4 Adverse Effects

The most common adverse reactions are related to dose-dependent vasodilation and include syncope, headache, and overt hypotension, emphasizing the need for adequate intravascular volume when initiating this agent. Electrophysiologic side effects include prolongation of the QT interval. Despite prolonging the QT interval, early studies have not demonstrated a significant proarrhythmic effect of levosimendan. Because of its vasodilating effects, levosimendan is contraindicated in patients with obstruction to ventricular filling or ventricular outflow.

20.6.2 Tolvaptan

The vaptans are arginine vasopressin receptor antagonists. Tolvaptan is a selective V_2 receptor antagonist that acts on the distal nephron to increase free water excretion (aquaresis) by blocking water reabsorption; this action helps correct heart failure-induced hyponatremia from excess ADH activity. In adults, tolvaptan was shown to improve symptoms of chronic heart failure and normalize serum sodium. Potential adverse effects include hypernatremia, dehydration, elevated aminotransferases, and elevated bilirubin. Unfortunately, an international phase 3 randomized trial evaluating the use of tolvaptan in pediatric patients with hyponatremia was terminated due to inadequate patient enrollment. A smaller pediatric study showed adverse events including thirst, dry mouth, and increased aminotransferases. A large adult study evaluating the use of tolvaptan in autosomal dominant polycystic kidney disease identified potential adverse effects including a transient increase in aminotransferases and bilirubin. Tolvaptan is not currently approved for pediatric use, but in several small investigational studies, it showed promise for the treatment of chronic heart failure in a select subset of patients.

20.6.3 Istaroxime

Istaroxime is a novel cardiovascular agent with both inotropic and lusitropic properties, at present studied only in adults and investigational in the United States (FDA granted fast-track designation in August 2019). The drug acts by improving cellular calcium cycling. Like digoxin, inotropic effects are achieved via Na^+/K^+ ATPase inhibition, which leads to cytosolic calcium accumulation in systole. Unlike digoxin, however, lusitropic effects are achieved via stimulating the enzyme responsible for sarcoplasmic reticulum sequestration of Ca^{2+} in diastole. In a study of adults with heart failure, istaroxime reduced pulmonary capillary wedge pressure, increased systolic blood pressure, decreased heart

rate, and decreased left ventricular end-diastolic volume. At higher doses, istaroxime improved cardiac index and stroke work index. Istaroxime had relatively few side effects and demonstrated a half-life of less than 1 hour. These preliminary findings suggest istaroxime may have efficacy, safety, and a pharmacokinetic profile amenable to its application in the pediatric population, though it has not yet been studied in children.

20.7 Use of Cardiovascular Agents in Septic Shock

The use of cardiovascular agents in septic shock has been studied extensively in adults, and recommendations were recently updated in the literature. An in-depth discussion regarding cardiovascular agent therapy in the context of septic shock can be found elsewhere in this text. (See ► Chap. 34, Sepsis, and ► Chap. 17, Circulatory Failure/Shock).

20.8 Control of Severe Hypertension

At times, the pediatric intensivist must obtain hemodynamic stability by controlling excessive arterial blood pressure. *Hypertensive urgency* is defined as severe hypertension without evidence of end-organ damage. *Hypertensive emergency* or crisis occurs when severe hypertension is associated with evidence of progressive end-organ dysfunction. Clinically, end-organ dysfunction may manifest as encephalopathy, retinal changes (hemorrhage, exudates, or papilledema), renal insufficiency (proteinuria and/or hematuria), microangiopathic hemolytic anemia, thrombocytopenia, and/or myocardial dysfunction. Without treatment, severe hypertension can produce catastrophic results such as intracerebral hemorrhage and/or left ventricular failure with pulmonary edema. Hypertensive emergencies require rapid but controlled reduction in blood pressure. This should occur in the intensive care unit, ideally with intra-arterial pressure monitoring since both oscillometric and manual blood pressure measurements are not reliable in this setting. Lowering the blood pressure by <25% in the first 8 h followed by a slower reduction over the next 24–48 h is generally recommended since more rapid reductions may result in ischemic stroke or ischemia in other organ systems that have adjusted their autoregulation to a higher blood pressure. Hypertensive urgencies should have blood pressure control achieved more gradually over 24–48 h.

A complete discussion of the epidemiology, clinical presentation, pathophysiology, and causes is beyond the scope of this section, which is focused on pharmacologic agents used to treat hypertensive emergencies. Regardless of the hypertensive state, a complete history and physical examination (including fundoscopic examination) combined with targeted laboratory tests and imaging is required to ascertain the etiology and end-organ effects of severe hypertension. This is of paramount importance as identifying the etiology allows appropriate tailoring of the therapeutic options. Primary hypertension is more common in older children, whereas secondary hypertension is more common in children <7 years of age. Common etiologies for severe hypertension in children are renovascular, intrinsic renal disease, drug effect (e.g., sympathomimetics, corticosteroids, or calcineurin inhibitors), and endocrine causes (e.g., pheochromocytoma, hyperadrenal states and hyperthyroidism).

There are no pediatric studies comparing antihypertensive agents in hypertensive emergencies, and drug and dosing recommendations are largely based on studies in adults.

Classes of antihypertensives include:

- Direct vasodilators (sodium nitroprusside, hydralazine)
- Calcium channel blockers (nicardipine, nifedipine, isradipine)
- Cardioselective β_1-adrenergic blockers (esmolol)
- Mixed adrenergic α-, β_1-blockers (labetalol)
- Selective α-adrenergic antagonists (phentolamine, phenoxybenzamine)
- Angiotensin-converting enzyme inhibitors (enalaprilat, enalapril, captopril)
- Angiotensin receptor antagonists (losartan, valsartan, olmesartan)
- Selective dopamine agonists (fenoldopam)
- Central α_2-adrenergic agonist (clonidine, dexmedetomidine)

Table 20.7 summarizes important properties of selected antihypertensives. A more detailed discussion of selected parenteral agents follows.

20.8.1 Nicardipine

20.8.1.1 Pharmacology

Nicardipine is a dihydropyridine calcium channel blocker that blocks a specific L-type Ca^{2+} channel that has a greater action on vascular smooth muscle instead of the heart. This channel blockade reduces movement of calcium into the cytoplasm of vascular smooth muscle producing selective arteriolar vasodilation (i.e., it has little effect on venous smooth muscle tone). The cerebral and coronary circulations are particularly sensitive to its effects. There is little effect on the heart.

Nicardipine has a rapid onset of action of approximately 5 minutes. Although its half-life is 40 minutes, its duration of action after discontinuation of a prolonged infusion may be 6 hours or more. Infusion rates range from 0.5 to 5 mcg/kg/min. Metabolism is hepatic with renal excretion.

20.8.1.2 Clinical Effects

Nicardipine promotes arteriolar vasodilation, thus reducing systemic vascular resistance with less reflex tachycardia than direct vasodilators. It also improves coronary blood flow and oxygen delivery and does not affect cardiac contractility.

20.8.1.3 Clinical Indications

Nicardipine's effectiveness, rapid onset, titratability, and safe therapeutic profile have made it an appropriate initial choice in a variety of hypertensive emergencies. It has been successfully used in children with hypertension secondary to renovascular disease, acute renal failure, post-coarctectomy, and hypertension secondary to calcineurin inhibitors or extracorporeal membrane oxygenation.

20.8.1.4 Adverse Effects

Nicardipine has become the preferred alternative to nitroprusside for the control of multiple types of pediatric hypertensive emergencies. The risk of thrombophlebitis with peripheral administration generally requires a large peripheral vein or central venous access for administration.

Thrombophlebitis has been reported with peripheral administration; therefore, large peripheral vein or central venous access is preferred. Like other nonspecific vasodilators, increased intrapulmonary shunt in children with preexisting parenchymal lung disease may occur due to uncoupling of hypoxemic pulmonary vasoconstriction. Nicardipine should be used with caution in children with conditions associated with raised ICP as cerebral vascular dilation may further increase intracranial pressure. It should be avoided in children with severe left ventricular outflow obstruction. Nicardipine-induced hypotension can be reversed with the administration of calcium and intravascular volume expansion.

Table 20.7 Parenteral agents for hypertensive emergencies

Agent	Mechanism of action	Usual dose	Onset/duration of action	Comments/cautions
Sodium nitroprusside	Nitric oxide donor – relaxes both venous and arterial smooth muscle	Infusion: 0.5–6 mcg/kg/min	30 seconds/2–3 min	May cause nausea, vomiting, reflex tachycardia and increased cardiac contractility, methemoglobinemia,
				Thiocyanate intoxication, lactic acidosis due to cyanide poisoning
				May increase intrapulmonary shunt or ICP
				Bags, bottles, and delivery sets must be light resistant
Nicardipine	Arteriolar vasodilator via calcium channel blockade in vascular smooth muscle	Infusion: 0.5–5 mcg/kg/min	2–5 min/40 min, but may be longer after prolonged infusion	May cause nausea, vomiting, or headache Phlebitis with peripheral administration so need central access
				Less reflex tachycardia than other vasodilators
				May increase intrapulmonary shunt or ICP
Esmolol	Cardioselective β_1 blockade	Initial 100–500 mcg/kg bolus	1–5 min/10–30 min	Rapid hydrolysis by RBC esterases
				Useful in post-coarctation repair
		Infusion: 25–300 mcg/kg/min		Use with caution with first-degree heart block, congestive heart failure, asthma
Labetalol	Mixed adrenergic blockade ($\beta_1 > \alpha_1$ blockade in ratio of 7:1)	Initial: 0.2–1 mg/kg, max. single dose 20 mg	5–15 min/2–6 hr	Hepatic metabolism allows use in children with renal insufficiency Use with caution with first-degree heart block, congestive heart failure, asthma, hepatic dysfunction
		Infusion: 0.25–3 mg/kg/hr		
Hydralazine	Direct arteriolar vasodilator	0.1–0.6 mg/kg/dose every 4-6 h prn Max single dose = 20 mg	10 min/2–6 hr after IV	Limited clinical usefulness due to unpredictable pharmacokinetics and risk of excessive drop in blood pressure. Useful in eclampsia – improves uterine blood flow
				May cause reflex tachycardia, headache, vomiting, increased ICP
Enalaprilat	Angiotensin-converting enzyme inhibitor	5–10 mcg/kg/dose every 8–24 hr up to 1.25 mg/dose	15–60 min/6 hr	Limited usefulness in hypertensive emergencies, second-line agent
				Useful in hyper-renin states
				Contraindicated in pregnancy, bilateral renal artery stenosis, chronic kidney disease and in states of decreased effective circulating volume
				Hyperkalemia possible with reduced GFR or with K^+ sparing diuretic
Fenoldopam mesylate	Selective dopamine (DA_1) agonist causing vasodilation of renal and splanchnic arterioles	Infusion: 0.05–0.3 mcg/kg/min	15 min/30 min	Useful in hypertension associated with renal insufficiency
				May cause headache, tachycardia, flushing, local phlebitis, increased intraocular pressure
Phentolamine	Selective α-adrenergic antagonist	0.05–0.1 mg/kg/dose, max 5 mg	1–2 min/30–60 min	Use limited to states characterized by catecholamine excess – specifically pheochromocytoma
				May cause reflex tachycardia, hypotension

20.8.2 Esmolol

20.8.2.1 Pharmacology

Esmolol is a highly selective β_1-adrenergic blocker that has a rapid onset (1–5 minutes) and short duration of action (15–30 minutes) making it an easily titratable antihypertensive. It is rapidly metabolized by red blood cell esterases allowing its use in children with renal and hepatic dysfunction.

Esmolol is a selective β_1 adrenergic blocker that has a rapid onset and short duration of action due to metabolism by RBC esterases, making it an easily titrated antihypertensive that can be used in children with renal and/or hepatic dysfunction.

Important drug-drug interactions include digoxin and morphine; digoxin levels should be followed closely as esmolol may increase digoxin levels by 20%. Morphine may increase esmolol effects; therefore, a decrease in esmolol dosing may be required. A starting dose of 50 mcg/kg/min can be titrated up to 300 mcg/kg/min.

20.8.2.2 Clinical Effects

By competitively blocking β_1 adrenoceptors, esmolol exerts negative inotropic and chronotropic effects. Its antihypertensive effects are due to a reduction in cardiac output; therefore, it should be used with caution and close monitoring in patients with preexisting myocardial insufficiency.

20.8.2.3 Clinical Indications

Esmolol has been used for the management of hypertension after pediatric cardiac operations, specifically coarctation of the aorta. It also may be effective in controlling hypertension and tachycardia in other situations characterized by excess sympathetic activity such as thyrotoxicosis and sympathomimetic overdose. It may be combined with a direct-acting vasodilator such as nitroprusside to blunt the peripheral vascular effects of reflex SNS activation as the blood pressure is reduced.

20.8.2.4 Adverse Effects

Like all β-blockers, esmolol should be used with extreme caution in children with a history of congestive heart failure, asthma, or conduction disturbances. Nausea, vomiting, dizziness, and confusion have been reported with prolonged or high-dose use.

20.8.3 Labetalol

A mixed adrenergic blocker, labetalol's antihypertensive effects are primarily from β_1 blockade causing a reduction in cardiac output and to a lesser extent α_1 blockade causing a reduction in systemic vascular resistance (β_1-to α_1-blocking activity is 7:1). In addition, labetalol has partial agonism for vascular β_2 receptors adding to its effect to lower systemic vascular resistance. Labetalol's β_1 blockade inhibits reflex tachycardia from a reduction in blood pressure. Labetalol has a rapid onset of action within 15 minutes of intravenous administration. Its prolonged duration of action up to 8 hours limits its titratability. Metabolism is hepatic, primarily via glucuronide conjugation with extensive first-pass effect.

An initial intravenous loading dose of 0.2–1 mg/kg can be followed by a carefully titrated infusion at 0.25–3 mg/kg/h, remembering that changes in the infusion rate will slowly reach a new steady-state concentration. Its hepatic metabolism allows for its use in children with renal dysfunction. Unlike direct vasodilators and calcium channel blockers, it does not appear to cause an increase in intracranial pressure, and thus, it is useful in patients with increased intracranial pressure. It should be used with caution in patients with first-degree heart block, congestive heart failure, asthma, and hepatic dysfunction.

20.8.4 Enalaprilat

The ACE inhibitor, enalapril, is converted in the liver to its active form, enalaprilat, which can be given intravenously. Unlike enalapril, enalaprilat has a rapid onset of action with a duration of 4–6 hours after a bolus. It is a second-line antihypertensive generally reserved for children suspected or known to have renin-mediated hypertension. Adult studies suggest this agent may be helpful in patients with hypertensive heart failure.

Since it lowers glomerular pressure and thus filtration by blocking the formation of angiotensin II, enalaprilat should not be used in children with bilateral renovascular hypertension or chronic kidney disease since it may cause acute kidney injury in these settings. Inhibition of angiotensin II reduces stimulation of aldosterone formation, so hyperkalemia may develop, especially in patients receiving potassium supplements. In patients whose blood pressure is highly dependent on activation of the renin-angiotensin system, an initial small dose should be infused and titrated upward since a large dose may cause profound hypotension. The usual dose is 5–10 mcg/kg/dose every 8–24 hr up to 1.25 mg/dose.

20.8.5 Fenoldopam

Fenoldopam is a selective postsynaptic dopamine DA_1 receptor agonist on vascular smooth muscle causing peripheral arteriolar vasodilation that is most pronounced in the renal and splanchnic vasculatures, but also increases coronary and cerebral blood flow. It promotes urine flow via improved renal perfusion and natriuresis. These characteristics make it of particular use in children with hypertensive emergencies associated with renal insufficiency. It is FDA-approved for short-term use in children with severe hypertension.

It has a rapid onset (~4 min) and short half-life (~5 min), but full extinction of effect may take up to 60 minutes. An initial infusion of 0.2 mcg/kg/min can be increased by 0.3–0.5 mcg/kg/min every 20–30 minutes (maximum dose: 0.8 mcg/kg/min). Tolerance develops rapidly; therefore, its use is limited to short-term (48 hours) control of blood pressure. Metabolism is hepatic via methylation, glucuronidation, and sulfation. Adverse effects include hypotension, hypokalemia, headache, nausea, dose-related tachycardia, flushing, local phlebitis, and increased intraocular pressure. To date, there are no large randomized controlled studies for the use of fenoldopam for pediatric hypertension.

Review Questions

1. *Dobutamine is started in a 16-year-old patient who presents with poor perfusion secondary to a previously unrecognized dilated cardiomyopathy. Which of the following statements is true regarding dobutamine?*
   A. Dobutamine selectively activates both β_1- and β_2-adrenoceptors with no effect at α-adrenoceptors.
   B. Dobutamine has important effects inhibiting thyroid and prolactin hormone release.
   C. Dobutamine is unlikely to cause tachyarrhythmias.
   D. Dobutamine's hemodynamic effects on vascular smooth muscle tone are difficult to predict since one isomer is an α_1-adrenergic agonist and the other is an α_1-adrenergic antagonist.
   E. Dobutamine is the drug of choice for treatment of cardiogenic shock.

2. *A 2-year-old near-drowning victim is brought to the PICU with poor perfusion, a low blood pressure, and a significant metabolic acidosis with a lactate concen-*

tration of 4.5 mmol/L. Which of the following statements is not true regarding the use of an epinephrine infusion in this setting?

A. An epinephrine infusion decreases plasma potassium concentrations through stimulation of β2-adrenoceptors.
B. An epinephrine infusion can complicate the interpretation of lactate concentrations since lactate levels often rise secondary to increased gluconeogenesis (Cori cycle).
C. Epinephrine is the drug of choice in postarrest cardiogenic shock because it better preserves myocardial blood flow and reduces myocardial metabolic demand.
D. When compared with norepinephrine, epinephrine is more likely to cause death or refractory cardiogenic shock with lactic acidosis in post-myocardial infarction shock.
E. An epinephrine infusion may redirect blood from the splanchnic circulation to the skeletal muscular vascular bed.

3. *To improve cardiac function in a child admitted with heart failure, an infusion of dobutamine is started. Dobutamine demonstrates high β_1 agonism. Which of the following statements accurately describes the effect of stimulation of myocardial β_1 adrenoceptors?*

A. Myocardial β_1 receptor binding results in the activation of a Gs protein which activates adenylate cyclase resulting in an increase in cytosolic cAMP.
B. Myocardial β_1 receptor binding results in the activation of a Gi protein which activates adenylate cyclase leading to increased cAMP.
C. Myocardial β_1 receptor binding results in the activation of a Gs protein that inhibits adenylate cyclase and, thus, cAMP formation.
D. Myocardial β_1 receptor binding results in the activation of a Gq protein which stimulates phospholipase C resulting in the formation of inositol triphosphate (IP_3).
E. Myocardial β1 receptor binding results in the activation of a Gs protein and the inhibition of adenylate cyclase leading to decreased cAMP.

4. *A child is admitted in status asthmaticus and started on continuous albuterol. Which of the following statements accurately describes the effect of stimulation of vascular and bronchial smooth muscle β_2-adrenoceptors?*

A. Vascular and bronchial smooth muscle β_2-adrenoceptor binding results in the activation of a Gs protein which activates adenylate cyclase leading to increased cAMP and increased protein kinase activity.
B. Vascular and bronchial smooth muscle β_2-adrenoceptor binding results in the activation of a G_i protein which activates adenylate cyclase leading to increased cAMP and increased protein kinase activity.
C. Vascular and bronchial smooth muscle β_2-adrenoceptor binding results in the activation of a Gi protein that inhibits adenylate cyclase, and thus, cAMP formation.
D. Vascular and bronchial smooth muscle β_2-adrenoceptor binding results in the activation of a Gq protein which stimulates phospholipase C resulting in the formation of inositol triphosphate (IP_3).
E. Vascular and bronchial smooth muscle β_2-adrenoceptor binding results in the activation of a Gs protein which stimulates phospholipase C resulting in the formation of inositol triphosphate (IP_3).

5. *Vasopressin is ordered for a child with renal insufficiency and low systemic blood pressure in the context of hepatorenal syndrome. Which of the following*

most accurately characterizes the effect of endogenous secretion of vasopressin?

A. It produces a vasopressin receptor-mediated improvement in cardiac contractility.
B. It results in a slowing of cardiac conduction via its effect on the atrioventricular node.
C. It results in adrenergic-mediated smooth muscle contraction.
D. It results in a receptor-mediated increase in chronotropy
E. Secretion may occur in response to either osmotic or nonosmotic stimuli.

6. *A 14-year-old presents with toxic shock syndrome due to osteomyelitis and Staphylococcus aureus bacteremia. His vital signs reveal a heart rate of 133 bpm, a blood pressure of 82/25 mmHg, and a respiratory rate of 30 breaths/min. Clinical exam reveals diffuse erythema, bounding pulses, and flash capillary refill. He receives aggressive fluid resuscitation with 0.9% normal saline (80 mL/kg) and has a central venous catheter placed. His plasma lactate concentration is 4.4 mmol/L with base deficit of 5.2 mmol/L, and his repeat blood pressure is 90/21. Which of the following is the most appropriate vasoactive infusion to initiate?*

A. Dobutamine
B. Dopamine
C. Norepinephrine
D. Epinephrine
E. Milrinone

7. *A 2-month-old infant is admitted to the PICU following patch closure of a large ventricular septal defect. She remains cool with poor distal pulses despite adequate volume resuscitation and an epinephrine infusion of 0.3 mcg/kg/min. Her current blood pressure is 98/64, her pulse is 168 bpm, and her pulmonary artery oxygen saturation is 53% with normal pulmonary artery pressure. An infusion of nitroprusside is initiated to decrease afterload. Which of the following is a characteristic of nitroprusside that would support its use in this setting, and what is a potential side effect of this medication?*

A. It has a rapid onset and short duration of effect; increased intracranial pressure
B. It has a direct effect on the distal collecting tubules promoting natriuresis; reflex bradycardia
C. It has a direct positive inotropic effect on the heart; increased intracranial pressure
D. It is metabolized by Hoffman degradation; methemoglobinemia
E. It slows atrioventricular cardiac conduction; thiocyanate intoxication

8. *A child is admitted to the PICU postoperatively status post-coarctation repair. An infusion of esmolol is administered. Esmolol is characterized by which of the following statements?*

A. It is a highly selective α_1-adrenoceptor antagonist with a rapid onset and short duration of effect and metabolism by hepatic glucuronide conjugation.
B. It is a highly selective β_1-adrenoceptor antagonist with a rapid onset and short duration of action and metabolism by hepatic glucuronide conjugation.
C. It is a mixed α_1-β_1-adrenoceptor antagonist with a rapid onset of effect, relatively long duration of effect, and metabolism by hepatic glucuronide conjugation.

D. It is a highly selective β_1-adrenoceptor antagonist with a rapid onset of effect, short duration of action, and metabolism by red blood cell esterases.
E. It is a nonselective β-adrenoceptor antagonist with a rapid onset of effect, short duration of action, and metabolism by red blood cell esterases.

9. *Nicardipine is considered for the treatment of a hypertensive emergency. Which of the following is a contraindication to the use of nicardipine?*
   A. Acute renal failure
   B. Left ventricular outflow tract obstruction
   C. Post-coarctectomy state
   D. Status post-extracorporeal membrane oxygenation
   E. Renovascular disease

10. *A 10-year-old boy is admitted to the PICU with severe hypertension. He is asymptomatic but was found to have a blood pressure of 212/100 mmHg and pulse of 100 bpm this morning when he presented to his pediatrician today for a school physical. Laboratory evaluation is unremarkable. A cardiac echocardiogram reveals a shortening fraction of 40%. A renal ultrasound is pending, and four extremity blood pressures are all elevated. Which of the following is the most appropriate treatment option while delineating the etiology of his hypertension?*
   A. Enalapril
   B. Esmolol
   C. Labetalol
   D. Nifedipine
   E. Nicardipine

11. *A 15-year-old male lacrosse player presents to the PICU with a thyrotoxicosis crisis following significant trauma to his anterior neck. His temperature is 104.8 °F, his heart rate is 190 bpm, and his blood pressure is 170/90 mmHg. He is very agitated and confused. Which of the following would be most indicated to control his symptoms, and which diagnosis in his past medical history would be concerning if prescribing this drug?*
   A. Clonidine, dry mouth
   B. Esmolol, asthma
   C. Enalaprilat, asthma
   D. Nicardipine, intrapulmonary shunt
   E. Nitroprusside, ventriculoperitoneal shunt

12. *A 5-year-old girl is admitted to the PICU with primary myocardial dysfunction due to cardiomyopathy. She is to be started on a milrinone infusion. Which of the following is an important consideration prior to initiating her infusion?*
   A. Intravascular volume status
   B. Relatively short half-life
   C. Mechanism of action as a β-adrenergic antagonist
   D. Its extensive hepatic metabolism
   E. Its negative lusitropic effects

13. *A 3-month-old baby boy is status post-cardiac catheterization during which he was diagnosed with anomalous origin of the left coronary artery arising from the pulmonary artery. He is noted to have severe left ventricular dysfunction. His pulse is 170 beats per minute and blood pressure is 80/65 mm Hg. He*

is cool to touch and has poor pulses. His central venous pressure measured at the superior cava – right atrial junction is 13 mm Hg. His hemoglobin is 10.5 gm/dL. He had been given furosemide earlier in the day. The most appropriate next step in the management of this infant is:

A. Administer a 20 ml/kg normal saline bolus
B. Administer a 10 ml/kg transfusion of packed red blood cells
C. Begin an epinephrine infusion at 0.2 mcg/kg/min
D. Begin a norepinephrine infusion at 0.1 mcg/kg/min
E. Begin a dobutamine infusion at 5 mcg/kg/min

14. *Which of the following statements best describe the overall hemodynamic results of isoproterenol?*
A. Decreased systemic vascular resistance
B. Increased inotropy and chronotropy with decreased systemic vascular resistance
C. Increased inotropy and chronotropy with increased systemic vascular resistance
D. Increased chronotropy
E. Increased inotropy

15. *What are two potential side effects of phentolamine?*
A. Tachycardia, hypotension
B. Tachycardia, hypertension
C. Bradycardia, hypotension
D. Hypertension, bronchoconstriction
E. Bradycardia, increased intracranial presssure

16. *Which of the following statements regarding vasodilators is true?*
A. Vasodilators routinely increase myocardial oxygen demand.
B. Nitroprusside selectively relaxes arteriole vascular tone with no effect on venous vascular tone.
C. Nitroglycerine is a useful vasodilator for long-term administration.
D. A vasodilator-induced increase in cardiac output is accompanied by an increase in venous return, even if the filling pressures (CVP, LAP) decrease.
E. Milrinone is a useful inodilator that has a short half-life making it useful for rapid titration to the desired hemodynamic effect.

Answers

1. D
2. C
3. A
4. A
5. E
6. C
7. A
8. D
9. B
10. E
11. B
12. A
13. E
14. B
15. A
16. D

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Mechanical and Electrical Myocardial Support

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Contents

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Learning Objectives

CPR

- Describe the physiologic basis of CPR.
- Explain the rationale underlying the selection of pharmacologic agents and doses.
- Explain why inpatient and out-of-hospital outcomes may differ.
- Describe the components of quality CPR.
- State the scientific reasoning behind the American Heart Association's most recent guidelines for the performance of pediatric basic and advanced life support.

ECMO

- Describe the difference between VV and VA ECMO.
- List three components of an ECMO circuit.
- Describe contraindications to the use of ECMO.
- Describe the outcomes after ECMO support.

Mechanical Assist Devices

- Describe the mechanics of mechanical assist devices: VADs and balloon pumps.
- Describe the indications for the use of a VAD.
- Describe complications associated with the use of a VAD.
- Discuss outcomes data of patients who require VADs.

Temporary Cardiac Pacing

- Describe the indication for using a temporary pacemaker.
- Describe the basic operations of a temporary pacemaker.
- Describe how to measure thresholds.

21.1 Cardiopulmonary Resuscitation

Cardiopulmonary resuscitation (CPR) and resuscitation medicine has progressed significantly in the past century. An explosion of interest in resuscitation in the mid-1900s led to important advancements in chest compressions and artificial respirations. The goal of CPR is to maximize coronary and cerebral blood flow and restore spontaneous circulation as soon as possible. The general principles of CPR remain the same; however, further investigations emphasized the importance of providing timely, high-quality CPR with limited hands-off time to improve patient outcomes. In this summary, we review the physiologic basis of CPR, detail the rationale for pharmacotherapy, discuss the outcomes for victims of pediatric cardiac arrest, and review the most recent American Heart Association guidelines.

21.1.1 Physiologic Basis of CPR and Patterns of Blood Flow

Three potential mechanisms are thought to support circulation during CPR: the cardiac pump, the thoracic pump, and the abdominal pump. The cardiac pump concept involves direct squeezing of the heart between the sternum and the spine leading to forward circulation via an open aortic valve and closed mitral valve, mimicking normal anatomic blood flow. This mechanism is thought to predominate in very young children due to their compliant thoracic wall, and in patients of all ages during open chest cardiac massage. The thoracic pump is a more likely mechanism in adults and older children during standard closed chest CPR. Increased intrathoracic pressure during chest com-

pression creates a pressure gradient between blood contained in structures within the thorax compared with extra thoracic blood vessels, which results in blood flow into the periphery. With the thoracic pump mechanism, the heart acts like a conduit with both the mitral and aortic valves open during chest compression. Releasing pressure on the chest in between compressions creates a negative subatmospheric intrathoracic pressure, which is lower than the pressure in the extrathoracic capacitance venous circulation so that the right heart fills prior to the next compression. The abdominal pump mechanism (i.e., abdominal compressions) is not invoked during standard chest compression CPR but is used in some CPR models to compress the abdominal aorta and inferior vena cava to respectively increase diastolic aortic pressure and venous return. There is insufficient evidence to recommend abdominal compressions in children.

21.1.2 Rationale of Pharmacotherapy for Patients with Cardiac Arrest

The initial study of the effect of epinephrine on cardiac output occurred in the 1870s when Pellacani administered adrenal extract to animals and observed increased arterial tone, ventricular contractions, and blood pressure. Since then, subsequent studies have demonstrated the importance of supporting diastolic blood pressure in the successful resuscitation of cardiac arrest. The heart is perfused through the coronaries only during diastole; thus, coronary perfusion is dependent on adequate diastolic blood pressure. Support of diastolic blood pressure, therefore, underlies the selection of pharmacologic agents during cardiac arrest. Standard code-dose epinephrine (0.01 mg/kg or 10 mcg/kg) remains the mainstay of cardiac arrest pharmacotherapy, with epinephrine's alpha-adrenergic vasopressor effects working primarily to augment aortic diastolic blood pressure. In a large analysis of in-hospital pediatric cardiac arrest, delays in epinephrine administration were associated with decreased chance of ROSC and decreased chance of survival. Randomized controlled trials of higher doses of epinephrine have not demonstrated any benefit, with a potential that high-dose (0.1 mg/kg) therapy worsens patient outcomes.

Epinephrine also augments inotropy and chronotropy via beta-adrenergic effects, which risks increasing myocardial oxygen consumption. To reduce this risk, efforts to identify an alternative agent with primary vasopressor properties without the potentially deleterious beta-adrenergic effects led to studies of vasopressin. Vasopressin acts on V1 receptors located on vascular smooth muscle, causing vasoconstriction via phospholipase C-phosphoinositide-mediated calcium release from intracellular stores. Low-dose vasopressin also causes vasodilation of cerebral and pulmonary circulations, potentially via the induction of nitric oxide release. A number of trials in adults failed to show a clear benefit of vasopressin over epinephrine, with a large pediatric cohort study associating vasopressin use with lower ROSC and a trend toward lower survival. There is insufficient evidence to make a recommendation for or against the routine use of vasopressin during pediatric cardiac arrest.

21.1.3 Outcomes After Cardiac Arrest

Pediatric cardiac arrest is a rare event, especially when compared to cardiac arrest in adults. The incidence of out-of-hospital cardiac arrest ranges from 2.6 to 19.7 annual cases per 100,000 children. ROSC is achieved in about 30% of

patients; however, only 24% of patients survive to be admitted to the hospital. Survival to discharge occurs in 8–12% of patients, with intact neurologic survival in only about 4% of patients. Survival differences exist between witnessed arrests (13% survival) compared to unwitnessed arrests (4.6% survival), indicating that earlier interventions may have important effects on long-term outcomes.

Outcomes from in-hospital pediatric cardiac arrest are better, with recent studies indicating 36–50% survival to hospital discharge. In one retrospective cohort multicenter study of inpatient pediatric cardiac arrest, 77% of cardiac arrest survivors were deemed to have a favorable neurologic outcome by the time of discharge, indicating that overall 37% of children who had suffered an in-hospital cardiac arrest had a good neurologic outcome. While differences likely exist in the baseline characteristics of children who suffer out-of-hospital versus those who suffer in-hospital arrests, the presence and availability of skilled providers capable of providing resuscitative efforts likely also contributes to the differences in outcomes. Nonetheless, even with expert resuscitation, cardiac arrest is a life-threatening event, with less than half of children surviving in-hospital cardiac arrest.

As with many aspects of pediatric medicine, efforts have shifted toward prevention and identification of hospitalized children who are clinically deteriorating. Rapid response teams have prevented cardiac and respiratory arrest, improved survival, reduced the need for ICU-level treatments following transfer, and decreased the time between patient deterioration and treatment.

Arrests are often preceded by several warning signs and symptoms. Studies are underway to evaluate the effectiveness of early warning systems such as the Pediatric Early Warning Scores (PEWS). Currently, there is limited evidence to suggest that the implementation of PEWS significantly reduces hospital mortality.

21.1.4 2015 AHA Pediatric Guidelines for Basic and Advanced Life Support for Healthcare Providers

The 2015 AHA guidelines for pediatric resuscitation transitioned from A–B–C (airway, breathing, circulation) to C–A–B sequences for all ages. The guidelines focus on calling for help, starting compressions early, and efficient treatment of dysrhythmias. For infants, the two-finger chest compression technique is recommended for single rescuer CPR, and the two-thumb chest-encircling technique recommended for two rescuer CPR. Compression-only CPR was studied in out-of-hospital pediatric cardiac arrest, with some studies indicating that it may be equally effective in children with a primary cardiac cause of arrest. However, considering most pediatric cardiac arrests are respiratory in origin, conventional CPR is recommended over compression-only CPR in the hospital environment. However, compression-only CPR may be a reasonable alternative in out-of-hospital cardiac arrest if it leads to increased bystander CPR, as lack of any bystander CPR is associated with worse outcomes.

The five components of high-quality CPR are (1) ensuring chest compressions at an adequate rate of 100–120 per minute; (2) compression depth of at least one-third the anterior-posterior diameter of the chest; (3) allowing full recoil between compressions; (4) minimizing interruptions in chest compressions; and (5) avoiding excessive ventilation. Unfortunately, CPR quality for in-hospital pediatric cardiac arrest often does not adhere to guidelines. Interruptions in compressions, including for rescue breaths, rhythm checks, and defibrillation attempts, lead to significantly decreased coronary perfusion

pressures and should be minimized. Leaning on the chest during CPR is common, even during in-hospital pediatric CPR, and was shown to decrease coronary perfusion pressure. Ensuring regular switches (approximately every 2 min) in chest compressors is recommended to decrease fatigue-associated leaning during CPR. Care should also be taken to avoid excessive ventilation, as this increases intrathoracic pressure, which impedes venous return and decreases cardiac output, as well as increasing the risk of stomach inflation leading to emesis and aspiration. An increase in end-tidal carbon dioxide ($ETCO_2$) during CPR reflects an increase in effective pulmonary blood flow, assuming that ventilation is held constant. Thus, monitoring $ETCO_2$ may be used to evaluate the quality of chest compressions. Since ROSC is characterized by a sudden increase in cardiac output, a sudden rise in $ETCO_2$ was shown to be a sensitive marker of ROSC. $ETCO_2$ during CPR may also offer limited prognostic information; however, specific target values have not been established in children.

The ratio of compression-to-ventilation for pediatric patients is 30:2 when a single health care provider (HCP) is present and 15:2 when two HCPs are present. Adult BLS guidelines apply for children at or beyond puberty, with a compression-to-ventilation ratio of 30:2 for one or two HCPs. If an advanced airway is placed, synchronized compression/ventilation cycles are no longer needed. Instead compressions are maintained at a rate of 100–120/min while ventilations are delivered at a rate of 8–10 breaths/min. CPR should continue until an AED or defibrillator arrives to check for the presence of a shockable rhythm. If a pulseless rhythm is found to be shockable (ventricular fibrillation or pulseless ventricular tachycardia), a first shock of 2 J/kg should be delivered, and CPR resumed immediately. After 2 min of CPR, the pulse and rhythm should be rechecked to determine the need for a subsequent shock of 4 J/kg, epinephrine, and continued CPR. The 2015 guidelines were updated to include lidocaine as an alternative to amiodarone for the treatment of ventricular tachycardia and ventricular fibrillation.

If bradycardia (<60 bpm) results in significant cardiopulmonary compromise (i.e., hypotension, signs of shock or acutely altered mental status) despite adequate oxygenation and ventilation, CPR should be initiated. Epinephrine remains the primary drug to treat pediatric bradycardia with compromised circulation; atropine is only reserved for cases when the bradycardia is believed to be secondary to excessive vagal tone or a primary AV conduction block. Persistent bradycardia unresponsive to ventilation, oxygenation, and medications is a potential indication for transcutaneous cardiac pacing (see Temporary Cardiac Pacing section).

Advanced airway placement during CPR allows continuous chest compressions; however, there is no clear benefit of endotracheal intubation over bag-valve-mask ventilation in out-of-hospital cardiac arrest. A laryngotracheal airway may provide a feasible alternative to endotracheal intubation, with some evidence that laryngotracheal airways confer a survival benefit in adult out-of-hospital arrest. Airway management ultimately depends on provider expertise and resources, with an emphasis remaining on avoiding interruptions in compressions.

Extracorporeal CPR (ECPR) may be considered for refractory cardiac arrest; however, studies found no overall benefit to ECPR compared with conventional CPR. However, compared with children with non-cardiac disease, children with underlying cardiac disease appear to have improved outcomes when ECPR is initiated in a critical care setting. Therefore, ECPR may be considered for pediatric patients with underlying cardiac disease suffering an in-hospital cardiac arrest.

Post-arrest care is focused on reversing the underlying disease process, optimizing end-organ perfusion, and avoiding secondary injury. While studies have

CPR most likely provides support during standard closed chest CPR by a "thoracic pump" mechanism in children and adolescents, whereas direct cardiac compression is likely important in infants and young children. The thoracic pump mechanism increases intrathoracic pressure during compression, which creates a pressure gradient that moves blood from the intrathoracic to extrathoracic compartments; releasing pressure in between compressions creates a subatmospheric intrathoracic pressure that helps refill the heart from blood in the higher pressure extrathoracic veins.

Supporting diastolic blood pressure is important during cardiac arrest, likely because coronary perfusion is dependent on diastolic blood pressure. At standard code-dose (0.01 mg/kg or 10 mcg/kg), epinephrine's predominant alpha-adrenergic vasoconstrictor effects augment aortic diastolic blood pressure.

The five components of high-quality CPR are (1) ensuring chest compressions at an adequate rate of 100–120 per minute; (2) depth of at least one-third the anterior-posterior diameter of the chest; (3) allowing full recoil between compressions; (4) minimizing interruptions in chest compressions; and (5) avoiding excessive ventilation.

Post-arrest care focuses on reversing the underlying disease process, optimizing end-organ perfusion, and avoiding secondary injury. There is no clear benefit to induced hypothermia following cardiac arrest, but fever (>38 °C) should be aggressively avoided.

Post-arrest, inspired oxygen concentration should be adjusted to achieve a pulse oximeter saturation between 94% and 99%.

not demonstrated a clear benefit to induced hypothermia following either in-hospital or out-of-hospital pediatric cardiac arrest, AHA guidelines recommend either maintaining 5 days of continuous normothermia (36 °C to 37.5 °C) or 2 days of initial continuous hypothermia (32–34 °C) followed by 3 days of continuous normothermia in comatose children following cardiac arrest. Fever (temperature > 38 °C) should be aggressively avoided. Given the potential oxidative stress of hyperoxia, inspired oxygen concentration should be weaned to maintain an oxyhemoglobin saturation of less than 100% but greater than 94%.

21.2 Extracorporeal Life Support

Veno-arterial extracorporeal membrane oxygenation (ECMO) is a form of prolonged cardiopulmonary bypass (CPB) that provides complete respiratory and cardiac support for critically ill patients with refractory cardiac and/or respiratory failure. Since 1990, over 60,000 patients have required ECMO for severe cardiopulmonary failure. Of those pediatric patients who received ECMO, greater than 70% survive to decannulation.

21.2.1 Mechanics of ECMO

A detailed physiologic description of ECMO is beyond the scope of this review. However, it is important conceptually to understand the means by which ECMO supports those with severe cardiac and/or respiratory failure. During ECMO, blood is removed from the venous circulation, oxygenated, and then returned to either a venous or arterial circuit. Veno-venous ECMO returns oxygenated blood to the venous circulation that is subsequently delivered to the pulmonary bed; systemic cardiac output depends on intact cardiac function and low pulmonary vascular resistance. Veno-arterial ECMO returns oxygenated blood to the systemic arterial circulation. ECMO flow can be supported through the use of either a roller or centrifugal pump. Data from the extracorporeal life support organization (ELSO) indicates that many institutions have converted to the use of centrifugal pumps for pediatric cardiac and respiratory ECMO, pediatric ECPR, and neonatal cardiac and ECPR. However, in neonatal respiratory failure, roller pumps are more commonly used. In comparison to roller pumps, centrifugal pumps are associated with increased hemolysis, hyperbilirubinemia, need for inotropic support, acute renal failure, and non-surgical bleeding. Contact of blood with the bioactive materials of the ECMO circuit is associated with an inflammatory response. Although controversial, pulsatile flow has been shown to better preserve the microvasculature, which may attenuate the systemic inflammatory response associated with EMCO.

21.2.1.1 Veno-Venous (VV) ECMO

VV ECMO has become the preferred mode of ECMO for respiratory support and should not be used for primary severe cardiac dysfunction. In VV ECMO the circuit is connected in series to the heart and lungs. Blood is removed from the venous circulation via a large catheter placed into the internal jugular vein, femoral vein, or the right atrial appendage for centrally cannulated patients. Blood is then pumped via a centrifugal or roller head pump through a membrane oxygenator, becomes highly oxygenated, and then is returned back to the venous circulation.

Systemic delivery of oxygenated blood is dependent upon adequate right-ventricular function, low pulmonary vascular resistance and left-atrial pres-

sure, and adequate left-ventricular function. Cannula placement and size must allow simultaneous venous drainage from and return to the patient's central venous circulation at sufficient flows to replace enough of the compromised lung function and maintain adequate oxygenation and ventilation. The efficacy of VV-ECMO can be affected by malpositioned cannulae that limit flow or increase recirculation of blood in the ECMO circuit. In contrast to VA ECMO, VV ECMO may result in recirculation, which occurs when oxygenated blood returning from the ECMO circuit is captured by the venous drainage port of the cannula without passing through the systemic circulation. Recirculation results in an increased monitored venous oxygen saturation noted in the venous drainage port and less than optimal tissue oxygenation. Determinants of recirculation include the cannula type and position along with the extracorporeal flow rate relative to the patient's cardiac output. Recirculation can be minimized by assuring optimal positioning of the bi-caval lumen catheter and avoidance of excessive ECMO flow rates. Specifically, with the bi-caval lumens, oxygenated venous return to the patient should be directed toward the tricuspid valve and the drainage holes should be oriented toward the lateral portion of the right atrium. The use of echocardiography and/or fluoroscopy can aid in optimizing catheter placement. High flow rates may increase streaming of oxygenated blood from the oxygen delivery port of the catheter to the venous drainage port.

21.2.1.2 Veno-Arterial (VA) ECMO

VA ECMO supports both the cardiac and respiratory systems. During VA ECMO, blood is removed from the venous circulation as seen with VV ECMO. However, after oxygenation the blood is returned to the aortic arch either through the common carotid artery, femoral artery, or directly to the aortic arch via central cannulation. With VA ECMO the circuit is connected in parallel to the heart and lungs. In comparison to VV ECMO, VA ECMO bypasses the pulmonary circulation in a flow-dependent manner resulting in a much higher arterial partial pressure of oxygen and oxygen delivery.

VA ECMO, especially pediatric peripheral VA ECMO, which most commonly uses the femoral vessels, may significantly increase left ventricular (LV) afterload through retrograde infusion of arterialized blood into the descending aorta. This increased afterload results in LV dilation and increased left ventricular and atrial pressures, which may cause hydrostatic pulmonary edema. To minimize LV overload and support recovery of the failing heart during VA ECMO, the failing LV may be unloaded by performing an atrial septostomy, which allows for left-to-right atrial flow, or by percutaneous or direct surgical venting of the LV.

21.2.2 Indications for ECMO

Indications for ECMO include hypoxemic or hypercapnic respiratory failure, circulatory failure, or a combination of both cardiac and respiratory failure. The use of ECMO for patients with cardiorespiratory failure should be deployed while recognizing that it does not treat the underlying illness. ECMO can be a bridge to recovery, a bridge to transplant, or a bridge to a ventricular assist device. Most contraindications are relative and patient specific. Relative contraindications may include the following: irreversible conditions; preexisting conditions which affect the quality of life; age and size of patient; and futility. Prolonged intubation and mechanical ventilation greater than 2 weeks also may be considered a potential contraindication. Caution should be taken

to employ ECMO in those with severe coagulopathy, concern for cognitive compromise prior to initiation of ECMO, or if the use of a ventricular assist device would be superior for the patient. With improvement in care and ECMO management, underlying illnesses such as malignancy and recent hematopoietic stem cell transplantation are not categorically seen as contraindications in the presence of a reversible illness such as acute respiratory distress syndrome.

21.2.3 Outcomes

Survival outcomes stratified by age and indication from 1989 to 2017 obtained from the Registry of the Extracorporeal Life Support Organization (ELSO) are summarized in ◘ Table 21.1.

21.2.3.1 Outcomes for ECMO Used for Respiratory Indications

Refractory neonatal respiratory failure is the largest single population in the ELSO registry and has the highest rate of survival. Since 1992, the rate of ECMO use for neonatal respiratory support has decreased by approximately 50%. This decline may be the result of improved technologies such as high-frequency ventilation, surfactant, and inhaled nitric oxide. The most common neonatal diagnosis requiring respiratory ECMO is congenital diaphragmatic hernia followed by meconium aspiration and persistent pulmonary hypertension. VA ECMO, through the internal jugular vein and carotid artery, remains the most common form of ECMO for neonatal respiratory failure. The most common complications for neonatal respiratory ECMO are cannula-related and intra-cerebellar hemorrhage.

The number of ECMO cases for pediatric respiratory extracorporeal life support continues to increase. Despite the increase in respiratory ECMO cases and complexity of patients supported, survival remains between 55–60%. The most common indication for pediatric ECMO is infectious pneumonias. Pediatric VA ECMO remains the predominate mode of cannulation. However, over the past decade VV ECMO is increasingly used. The mean duration of respiratory ECMO is longer than ECMO used for myocardial support. Mechanical complications such as oxygenator or cannula malfunctions are more common in pediatric respiratory ECMO than patient-related complications. However, mechanical complications are associated with a lower mortality than those suffering patient-related complications. The most common

◘ **Table 21.1** ECMO outcomes by etiology and age

	Cases (*n*)	Survived ECMO *n* (%)	Survived to discharge or transfer *n* (%)
Neonatal			
Respiratory	30,062	25,297 (84)	22,040 (73)
Cardiac	7242	4697 (65)	2988 (41)
ECPR	1554	1048 (67)	641 (41)
Pediatric			
Respiratory	8162	5487 (67)	4699 (58)
Cardiac	9479	6482 (68)	4844 (51)
ECPR	3469	1995 (58)	1444 (42)

patient-related complication was intracranial hemorrhage, which is associated with a 79% mortality rate.

Factors associated with hospital mortality for patients receiving ECMO for respiratory failure include age, pulmonary diagnosis, concurrent organ dysfunction, severity of ventilator-associated lung injury prior to ECMO, and mode of ECMO. Increased mortality was associated with age >10 years, pertussis, sepsis, opportunistic infections, renal failure, hepatic injury, immunodeficiency, cardiac arrest prior to ECMO, severe acidosis, high mean airway pressures, duration of mechanical ventilation >14 days prior to ECMO, and the use of VA ECMO.

Increased survival was observed in those patients with a younger age, asthma, viral pneumonia or bronchiolitis, aspiration pneumonia, absence of concurrent organ dysfunction, and the use of VV ECMO.

21.2.3.2 Outcomes for ECMO Used for Cardiac Indications

Over the past several decades, the use of ECMO in both neonates and pediatric patients for cardiac failure continues to increase. Survival to discharge for cardiac ECMO is less than that seen for respiratory ECMO but has remained constant between 40% and 50%. In contrast to neonatal cardiac ECMO, pediatric cardiac ECMO patients usually have a longer average ECMO duration and better survival.

Congenital heart disease is the most common indication for neonatal and pediatric cardiac ECMO. Patients with hypoplastic left heart syndrome have the longest duration of ECMO and the lowest survival rate, while those pediatric patients with right-sided obstructive lesions have shorter ECMO runs and a higher survival. Neonates with cardiomyopathy or myocarditis have a higher rate of survival. Among pediatric cardiac ECMO patients, those with myocarditis have the highest survival rate.

Bleeding at the surgical site is common and occurs approximately in 25% of both neonatal and cardiac patients requiring cardiac ECMO. Intracranial pathology, cerebral infarction, or intracranial hemorrhage is associated with reduced survival in both neonates and children.

During ECMO blood is removed from the venous circulation, oxygenated, and then returned to either the venous or arterial circuit (i.e., veno-venous or veno-arterial ECMO, respectively).

ECMO for patients with cardiorespiratory failure should be deployed recognizing that ECMO supports the cardiorespiratory system, but does not treat the underlying illness.

ECMO is used as a bridge to recovery, a bridge to transplant, a bridge to provide time for a decision to be made, or a bridge to a ventricular assist device (i.e., destination therapy).

21.2.4 Extracorporeal Cardiopulmonary Resuscitation (ECPR)

ECMO cannulation during active chest compressions is termed extracorporeal cardiopulmonary resuscitation (ECPR). ECPR is increasingly being deployed as an adjunct to conventional CPR. Currently there is insufficient evidence to recommend the use of ECPR for pediatric out-of-hospital cardiac arrests. When ECPR is used during in-house pediatric cardiac arrest, the outcome for children with underlying cardiac disease is better than for those with non-cardiac disease. In centers where rapid initiation of ECMO is possible, ECPR may be considered in children with cardiac disease following in-house cardiac arrest. Compared with ECMO for cardiac and/or respiratory failure, the overall survival for ECPR is lower in both neonatal and pediatric patients undergoing ECPR.

Non-cardiac diagnosis, pre-arrest renal insufficiency, and longer duration of CPR prior to ECMO initiation are all associated with an increased odds of death. Adverse events including neurologic, pulmonary, renal, metabolic, cardiovascular, and hemorrhagic occurring during ECMO are also associated with increased odds of death with higher odds occurring when multiple adverse events are documented during ECMO.

Recirculation is a phenomenon in which reinfused oxygenated blood during VV ECMO is withdrawn by the drainage cannula without passing through the systemic circulation, which decreases the efficiency of VV ECMO. If repositioning the cannula does not reduce recirculation, the ECMO flow rate may need to be reduced.

Neonatal respiratory failure is the most common indication for ECMO and has the highest rate of survival.

When ECPR is used during in-house pediatric cardiac arrest, the outcome for children with underlying cardiac disease is better than for those with non-cardiac disease.

21.3 Mechanical Assist Devices

Although the development of pediatric mechanical circulatory support devices has lagged behind that of adults, the gap between them is steadily closing. The type of pediatric mechanical circulatory support selected is determined by the type of organ support needed, anticipated duration of support, patient's body size, and the goal of mechanical circulatory support (recovery, destination, or transplant). Mechanical circulatory support options in children include ECMO, intraaortic balloon pumps (IABP), and ventricular assist devices (VADs). VA ECMO remains the most common form of mechanical support allowing for complete cardiopulmonary support. As previously noted, VV ECMO is indicated for patients with severe respiratory failure. Classically VA ECMO has been utilized for cardiopulmonary support whereas VADs have been used solely for cardiac support. In contrast to VA ECMO, single ventricle VADs require an adequate degree of native cardiac and lung function. Within the past several years, there are case reports describing the use of oxygenators in combination with biventricular VADs to provide adequate oxygenation and ventilation.

21.3.1 Intraaortic Balloon Pumps (IABP)

The use of an IABP in a pediatric patient was first described in 1989. A balloon pump can be inserted peripherally or centrally and consists of a long balloon positioned in the descending aorta. Balloon timing is synchronized with ventricular diastole and systole. The balloon is inflated during ventricular diastole and deflated during ventricular systole (Fig. 21.1). During inflation (ventricular diastole) the balloon enhances coronary perfusion by displacing aortic blood into the coronary circulation as well as facilitating antegrade blood flow, while during deflation (ventricular systole), ventricular afterload is reduced by

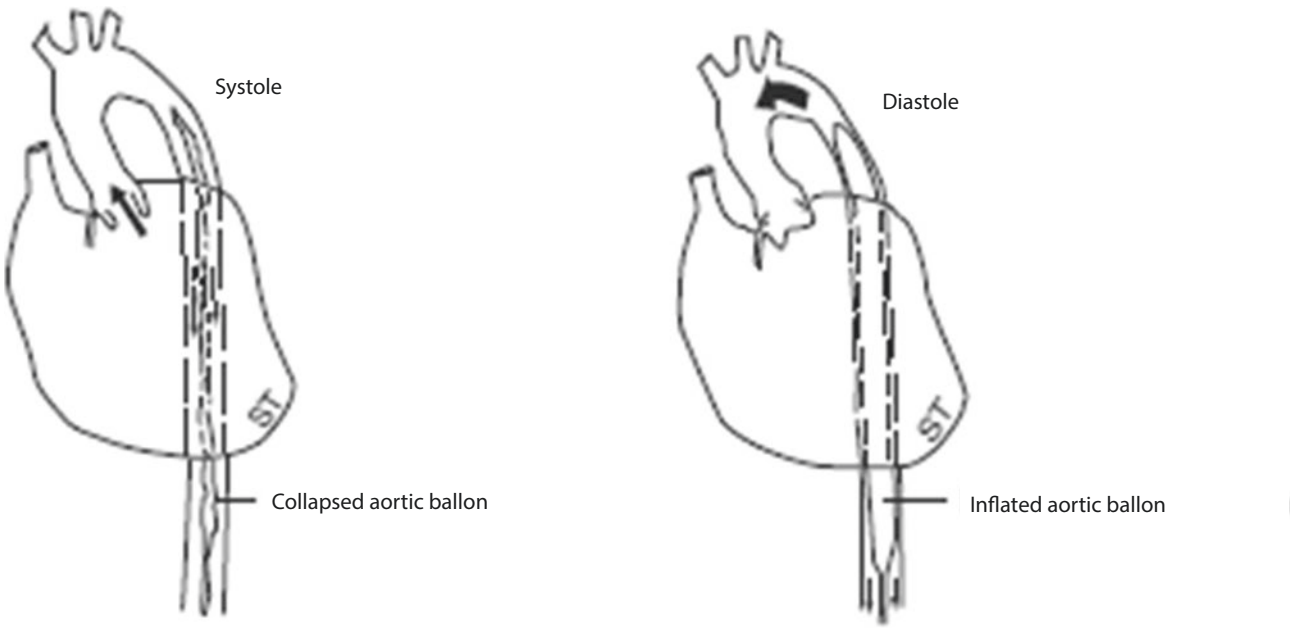


Fig. 21.1 Intraaortic balloon pump position during diastole and systole. Note that inflation during diastole increases diastolic pressure and displaces blood from the aorta into the coronary circulation

creating an "empty" space in the aorta that is filled by ventricular contraction. The reduced afterload enhances ventricular emptying (i.e., increases stroke volume) and reduces ventricular wall stress by reducing end-diastolic pressure and volume.

IABP provides support only to the left ventricle and is indicated for those conditions associated with left heart failure. Unfortunately, balloon size and the increased compliance of the juvenile aorta limit the use of balloon pumps in pediatric patients. The usage of IABPs for temporary circulatory support in children has not been widespread. Balloon pumps may be reasonable for short-term support in larger children and adolescents with isolated left heart failure. Complications following IABP include sepsis, bleeding, and transient limb, mesenteric, renal, and celiac artery ischemia.

21.3.2 Ventricular Assist Devices (VADs)

VADs are designed to assist either the right ventricle (RVAD), the left ventricle (LVAD), or both ventricles (BiVAD). The type of ventricular assistance device applied depends upon the type of underlying heart disease and pulmonary arterial resistance. RVADs pump blood from the right atrium or ventricle to the pulmonary artery whereas LVADs pump blood from the left ventricle to the aorta. BiVADs are composed of two separate devices: one for support of the RV and one for support of the LV. For patients with minimal native cardiac function and no hope for a recovery, a BiVAD or total artificial heart (TAH) can be used to replace all functions of the native heart. Left VADs (Fig. 21.2) are the most commonly used support devices in pediatrics followed by BiVADs. RVADs and total artificial hearts are infrequently used in pediatric patients.

Initially, VADs were classified according to blood flow characteristics, placement of the VAD in relation to the patient, and the duration of intended use. Blood flow can be pulsatile or continuous. Placement could be intracorpo-

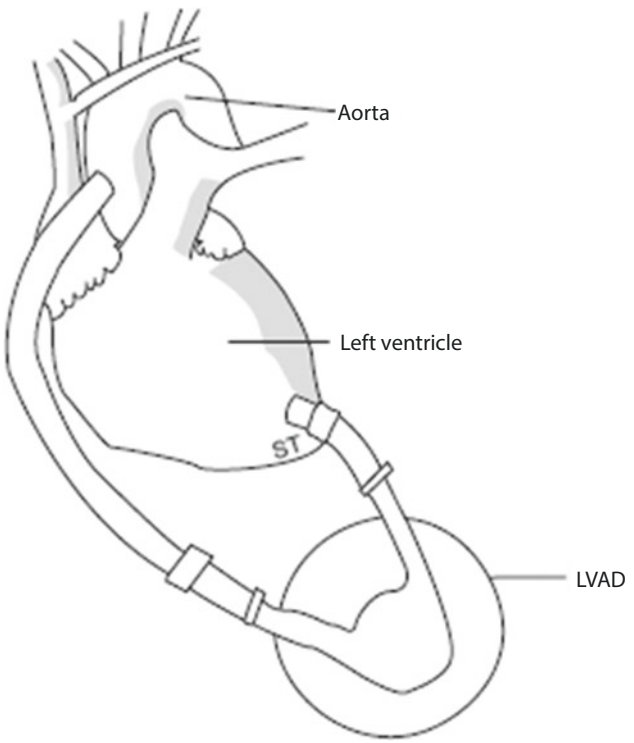


Fig. 21.2 Left ventricular assist device (LVAD)

Table 21.2 Summary of VAD types and devices

VAD type	Device brand
Paracorporeal pulsatile	AbioMed AB 5000, Berlin Heart EXCOR, Thoratec PVAD
Paracorporeal continuous	Thoratec Centrimag & Pedimag, Maquet Rotaflow, Sorin Revolution
Implantable continuous	HeartWare HVAD, HeartMate II LVAD, HeartMate III
Percutaneous	Abiomed Impella 2.5/5.0 & CP, Tandem Heart
Total artificial heart	Syncardia Total Artificial Heart

real, paracorporeal, or percutaneous. Currently, there is a trend toward using devices previously defined as temporary for long-term support. As a result, categorization of device type is now based on design and flow characteristics. Device brands based on design and flow characteristics categories are summarized (Table 21.2)

The first VAD used in a pediatric patient was the Berlin EXCOR pulsatile pump, which is currently the only Food and Drug Administration (FDA)-approved pediatric VAD available in the United States and the only long-term VAD available for newborns and infants; the device is also available for children and adolescents. Device selection differs significantly by the age of the patient and is often a reflection of patient size limitations for implantation. In children weighing less than 20 kg or less than 5 years old, paracorporeal continuous and paracorporeal pulsatile devices are almost exclusively used. Considering all patients less than 19 years of age, intracorporeal continuous flow devices are the most commonly used, followed by paracorporeal pulsatile and paracorporeal continuous flow devices. Percutaneous and total artificial hearts are infrequently used in pediatric patients.

21.3.2.1 Impella (Abiomed Inc.)

The Impella is a temporary percutaneous VAD consisting of an axial flow pump that crosses the aortic valve to unload the left ventricle by delivering nonpulsatile blood flow to the ascending aorta. The Impella has been used for short-term circulatory support in children and adolescents with refractory or ongoing cardiogenic shock, following an acute myocardial infarction, or following open heart surgery. In contrast to VA ECMO, the Impella provides both hemodynamic support and cardiac unloading. The benefits of left ventricular volume unloading include reduction in LV wall stress, improvement in coronary blood flow, and reduced myocardial oxygen consumption. As noted previously, VA ECMO may increase left ventricular afterload and inadequately decompress the left ventricle, especially in patients without a left atrial vent or septostomy and severely depressed systolic function. Reported complications include device malfunction, limb ischemia, vascular injury, hemolysis, bleeding, and infection.

21.3.2.2 TandemHeart (CardiacAssist, Pittsburgh, Pennsylvania, United States of America)

The TandemHeart VAD is an external centrifugal pump traditionally used in adults with heart failure. In adults, the TandemHeart device may be placed percutaneously with an inflow cannula placed transeptally into the left atrium and an outflow cannula placed into the femoral artery. In children, the TandemHeart has been surgically placed via central cannulation similar to ECMO. However, most temporary VADs do not support oxygenation and

require a high minimum flow rate. In pediatrics, several reported circuit modifications to the TandemHeart have been performed to provide lower flow including recirculation shunts, flow occlusion clamps, and, in some cases, an oxygenator. Within the last decade these modifications have allowed for the successful use of the TandemHeart in neonates, infants, and children.

21.3.3 Indications for Use of a VAD

Cardiomyopathy is the most commonly indicated diagnosis, followed by congenital heart disease and myocarditis. VADs can be used as a bridge to heart transplant, to recovery of heart function, or as permanent support for the failed heart (i.e., destination therapy). The primary indication for VAD use in pediatric patients is a bridge to transplant. VAD implantation as a bridge to recovery or destination therapy continues to be infrequent in children.

Contraindications for VAD therapy include significant preexisting neurologic injury, very low birth weight <2 kg, and life-limiting congenital or major chromosomal anomalies. Multisystem organ failure may also be considered a contraindication if organ function is not predicted to be reversible following hemodynamic improvement via the VAD.

21.3.4 Complications Associated with the Use of a VAD

The most frequent complications associated with pediatric VAD use are infection, neurologic dysfunction, and bleeding. Common neurologic complications include stroke, subarachnoid hemorrhage, and seizures. Independent of device type, infection, bleeding, and stroke tend to occur within the first 90 days of support. Reported differences in adverse event rates noted amongst different devices may be due to major differences in the patient population rather than the device type.

21.3.5 Outcomes of Patients Who Require VAD

The Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) is a National Heart, Lung, and Blood Institute-supported North American registry. Pedimacs was developed in 2012 to serve as a comprehensive registry for temporary and durable VADs in children and adolescents <19 years of age. The third annual Pedimacs report summarizes the most current data between September 2012 and December 2017. During this time span, 30 institutions implanted 508 devices in 423 patients. Dilated cardiomyopathy was the most commonly indicated diagnosis, followed by congenital heart disease, and myocarditis. The majority of children with congenital heart disease have single ventricle anatomy.

Actuarial survival of all pediatric VAD patients at 6 months is approximately 74%. Older patients (aged 11–19 years old) have a higher actuarial survival (86%) at 6 months compared with patients less than 1 year of age (50%), who have the highest mortality.

Differences in survival based on device type may reflect differences in age and severity of illness rather than device-specific outcomes. For example, paracorporeal devices that are mostly used in smaller, younger, and more ill patients are associated with a higher earlier mortality compared with intracorporeal devices that are predominantly used in older and less ill patients. Early death is associated with cardiogenic shock, the use of BiVAD, percutaneous devices, paracorporeal continuous devices, smaller volume, younger age, and low weight.

The type of pediatric mechanical circulatory support selected is determined by the type of organ support needed, anticipated duration of support, patient's body size, and the goal of mechanical circulatory support (recovery, destination, or transplant). Mechanical circulatory support options in children include ECMO, intraaortic balloon pumps (IABP), and ventricular assist devices (VADs). ECMO remains the most common form of mechanical support.

During inflation (ventricular diastole) the intraaortic balloon enhances coronary perfusion while during deflation (ventricular systole), ventricular afterload is reduced.

The primary indication for VAD use in pediatric patients is a bridge to transplant and cardiomyopathy is the most commonly indicated diagnosis.

Differences in adverse event rates noted amongst different devices may be due to major differences in the patient population rather than the device type.

Differences in survival based on device type may reflect differences in age and severity of illness.

Survival outcomes stratified by diagnoses are superior in patients with cardiomyopathy compared with those patients with congenital heart disease who tend to have a higher severity of illness.

Neurologic dysfunction and multisystem organ failure are the most common causes of death in patients receiving paracorporeal continuous and paracorporeal pulsatile devices. Neurologic dysfunction is the most common cause of death in patients supported by implantable continuous devices.

21.4 Temporary Pacemakers in the PICU

A temporary cardiac pacemaker is a device that delivers electrical stimulation to the heart resulting in a propagated electrical impulse that results in cardiac contraction. A pacemaker can initiate or maintain a heart rate or overdrive pace a tachyarrhythmia. Temporary leads may be in direct or close contact with the heart in multiple ways: transcutaneous (ventricular pacing only), transvenous, epicardial, or trans-esophageal (atrial pacing only).

In the PICU, temporary cardiac pacing is often performed using epicardial wires placed by the cardiothoracic surgeon usually at the time of surgical palliation or repair of a congenital heart defect. Epicardial temporary pacemakers can pace the atrium if the patient has intact atrioventricular conduction, or the ventricle to provide a minimum ventricular rate in the presence of complete heart block. Dual-chamber pacemakers can pace either or both the atrium and the ventricle, therefore providing atrioventricular (AV) synchrony. Temporary pacemakers are often used to treat symptomatic bradyarrhythmias frequently due to transient postoperative atrioventricular (AV) nodal block. Surgically acquired heart block persisting beyond 14 days is likely to be permanent.

Temporary atrial pacing wires may be used to help the clinician diagnose arrhythmias by obtaining a pure atrial electrogram on a 12-lead electrocardiogram (ECG). An atrial ECG is extremely helpful when P waves are not clearly visible on the surface electrocardiogram. The most useful way to perform an atrial electrogram is to attach the atrial wires to the right-arm and left-arm ECG leads, which will produce a bipolar atrial electrocardiogram in lead I and a unipolar atrial electrocardiogram in the remainder of the limb leads (see Fig. 21.3a, b, Atrial electrocardiogram).

Another useful application of temporary atrial pacing wires is to treat tachyarrhythmias. In junctional ectopic tachycardia the atrial wire may be used to pace faster than the tachycardia (over drive pace) and provide an atrial kick. In reentry supraventricular tachycardia, such as atrial flutter and atrioventricular reciprocating tachycardia, overdrive pacing may terminate the tachycardia. Typically, the pacing rate is set at 10–20 beats faster than the tachycardia rate with pacing intervals at 5–20 s in duration. Multiple attempts with progressively faster rates can be attempted to terminate the tachyarrhythmia.

21.4.1 Normal Cardiac Conduction

The cells in the cardiac myocardium have properties of automaticity. The fastest site of cardiac automaticity will act as the intrinsic cardiac pacemaker. Under normal conditions this site is the sinoatrial (SA) node which is an epicardial structure located near the junction of the superior vena cava (SVC) and the right atrium (RA). The electrical impulse spreads across the RA and

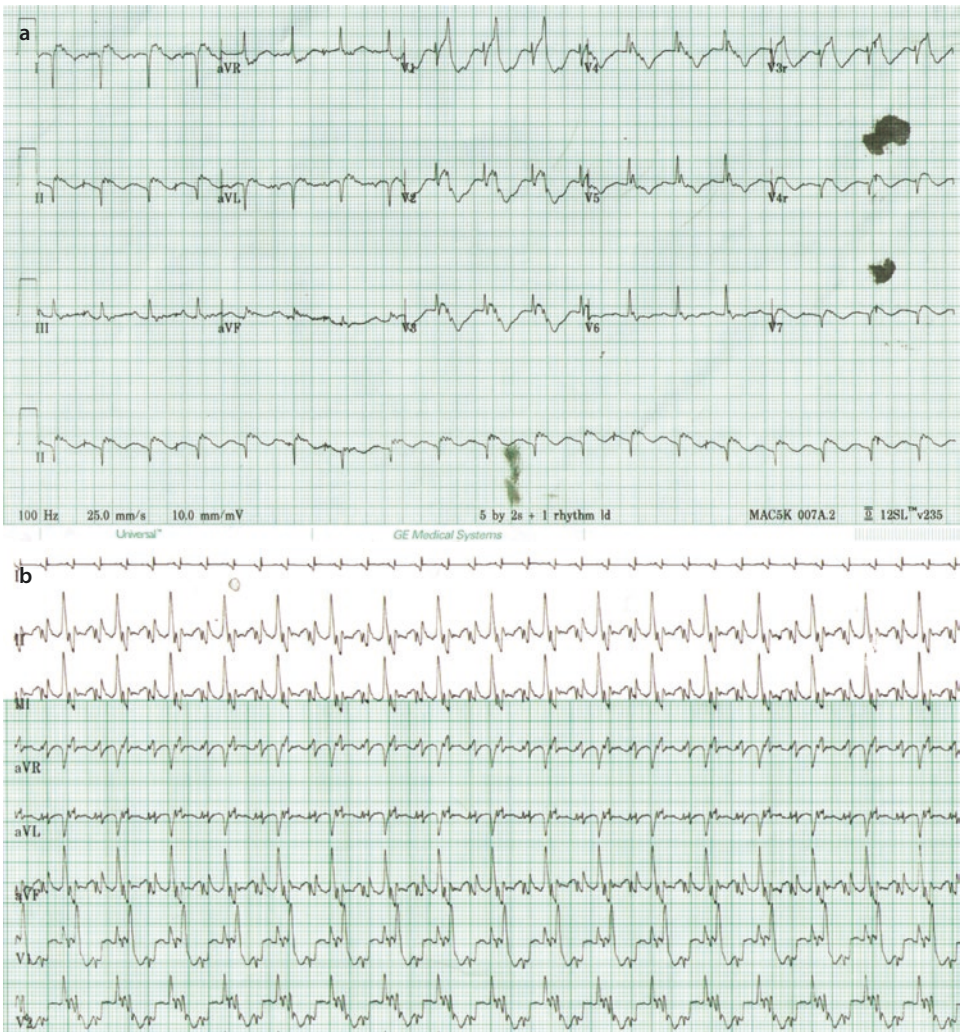


Fig. 21.3 Atrial electrocardiogram. A. Surface electrocardiogram of a patient with Ebstein's anomaly following tricuspid valve replacement who now has an intra-atrial reentry tachycardia with 2:1 AV conduction. The P waves are not clearly seen B. Atrial electrocardiogram of the same patient shows the P waves with 2:1 AV conduction more clearly

through fibers of tissue known as Bachman's bundle to the left atrium. This electrical impulse causes atrial depolarization. The electricity pauses for a fraction of a second at the atrioventricular (AV) node, which acts as a gatekeeper from the atrial to ventricular chambers. Following conduction through the AV node, electricity travels through the His and right and left bundle branches, which causes ventricular depolarization.

21.4.2 Special Considerations for Pediatric Patients

Sinus node dysfunction is rare in the pediatric population but may occur in newborns or infants with the left atrial isomerism variation of heterotaxy since the SA node is missing. Symptomatic bradycardia is more likely due to disease/injury of the AV node. Causes of AV node disease/injury include those that are surgically acquired, drug-induced dysfunction, rheumatic heart disease, Lyme disease, myocarditis, cardiomyopathy, or acute rejection in heart transplant. Patients born with ventricular inversion (L-transposition of the great vessels) have a high risk of AV block throughout their life. The finding of complete heart block is often the presenting finding prior to the diagnosis of isolated

ventricular inversion. There is a risk for operative AV block in any patient undergoing cardiac repair of a defect located near the normal conduction system including aortic, mitral, or tricuspid valve surgeries; ventricular septal defect repair, atrioventricular septal defect repair; or repair of congenitally corrected transposition of the great arteries. In a patient undergoing repair of a cardiac defect with concurrent L-transposition of the great vessels, the risk of postoperative AV block is significantly higher. If surgically acquired heart block persists for more than 14 days, it is likely to be permanent. Temporary epicardial pacing can be used to bridge this interval between intermittent postoperative heart block and recovery of spontaneous conduction; otherwise permanent postoperative heart block requires permanent pacemaker implantation.

Junctional ectopic tachycardia (JET) is sometimes seen as a transient arrhythmia in the immediate postoperative period. It is thought to arise from abnormal automaticity near or within the AV node secondary to stimulation or inflammation associated with surgery in this region. Mildly elevated junctional rates are often well tolerated; however, loss of AV synchrony may be detrimental to some patients in the immediate postoperative period. Atrial overdrive pacing at a slightly faster rate (5–10 beats over the actual JET-rate) may reestablish AV synchrony and improve ventricular filling with the atrial contraction ("atrial kick"). This is usually performed using the temporary atrial pacing wires placed during surgery but may also be accomplished by trans-esophageal pacing of the atria. The pacing rate needs to be continuously adjusted during the treatment of JET to provide the minimal necessary pacing rate.

Children have relatively small blood vessel diameters; therefore, in infants and small children, an epicardial pacing system is preferred over a transvenous endocardial system. Placement of transvenous pacemaker leads in smaller patients may lead to venous congestion or occlusion and preclude future transvenous lead placement. Transvenous pacing leads should not be placed in patients with intracardiac shunts secondary to the risk of paradoxical emboli to the systemic circulation.

Recent literature suggested a benefit to simultaneous pacing of both ventricles compared to conventional right ventricular pacing. This may be performed when the surgeon places a right ventricular and left ventricular epicardial lead at the time of surgery and both wires are connected to the same pacemaker pulse generator. The literature has suggested that this may be especially beneficial in improving cardiac performance if there is a need for temporary pacing after repair of congenital heart disease. Biventricular pacing may also improve pacing-induced ventricular dysfunction associated with right ventricular pacing. Biventricular pacing requires evaluation and adjustment of the threshold energy required on each ventricular lead separately. The final pacemaker ventricular output should be based on the ventricular lead with the highest threshold. In general, the ventricular output should be set 2–3 times greater than the threshold.

21.4.3 Which Temporary Pacemaker Should Be Used?

Choice of the temporary pacemaker settings depends on the clinical situation and the underlying conduction defect. Patients with symptomatic bradycardia (secondary to heart block, sick sinus syndrome, or drugs) may benefit from single-chamber pacing to provide a steady baseline heart rate. With symptomatic sinus bradycardia or sick sinus syndrome and intact AV conduction, single-chamber atrial pacing is preferred. Patients with transient heart block usually have a normal atrial rate and a slow ventricular escape rate. In this situation, hemodynamics are optimized if a dual-chamber pacemaker is used to sense ("track") the intrinsic atrial electrical activity, and sequentially pace the ven-

tricle accordingly. Dual-chamber pacing mimics normal cardiac electrical activity and augments cardiac output by improving ventricular filling with the atrial contraction ("atrial kick") preceding ventricular systole. This is especially important in patients with single ventricle physiology.

21.4.4 Types of Temporary Pacemakers

There are single-chamber and dual-chamber temporary pacemakers. The most commonly used ones are: Medtronic models 5348 (single-chamber) and 5388 (dual-chamber) and St. Jude Medical models 3077 (single-chamber) and 3085 (dual-chamber).

21.4.5 Use of Controls

Caution: Always learn the specific model in your unit before using it on your patient.

21.4.5.1 Single-Chamber Pacemaker

The basic controls on a single-chamber pacemaker include rate (pulse per minute, ppm), output (milliamps, mA), and sensitivity (millivolts, mV). Most temporary models are also able to deliver rapid atrial pacing (RAP) for overdrive atrial pacing to attempt to terminate JET or reentry supraventricular tachycardia (atrial flutter, intra-atrial reentry tachycardia, atrioventricular reciprocating tachycardia, and atrioventricular nodal reentry tachycardia). A rapid atrial pacing rate of up to 800 pulses per minute (ppm) is possible but rates beyond 400/min are rarely used. Modes are designated by a three-letter code corresponding to chamber paced, chamber sensed, and response to sensing (Table 21.3). Mode choices for single chamber temporary pacemakers include: VVI, VOO, AAI, and AOO.

21.4.5.2 Dual-Chamber Pacemaker

The controls for dual-chamber pacemakers follows the basic principles of a single-chamber pacemaker. There are three main controls: rate (ppm), atrial output (mA), and ventricular output (mA). In the secondary menu, in the lower half in the Medtronic model (Fig. 21.4), and adjacent to the major dials on the Abbott/St. Jude Medical model, atrial and ventricular sensitivity and AV interval can be adjusted. The rate and AV delay can be set to maximize cardiac output for a patient's age and clinical status. In general, the AV delay is set between 100–140 ms in most children. Post-ventricular atrial refractory period (PVARP) can also be adjusted. RAP is also available with most dual-

Table 21.3 Standard nomenclature for pacemaker modes

I Chamber paced	II Chamber sensed	III Response to sensing
0 = none	0 = none	0 = none
A = atrium	A = atrium	T = triggered
V = ventricle	V = ventricle	I = inhibited
D = dual (A + V)	D = dual (A + V)	D = dual (T + I)

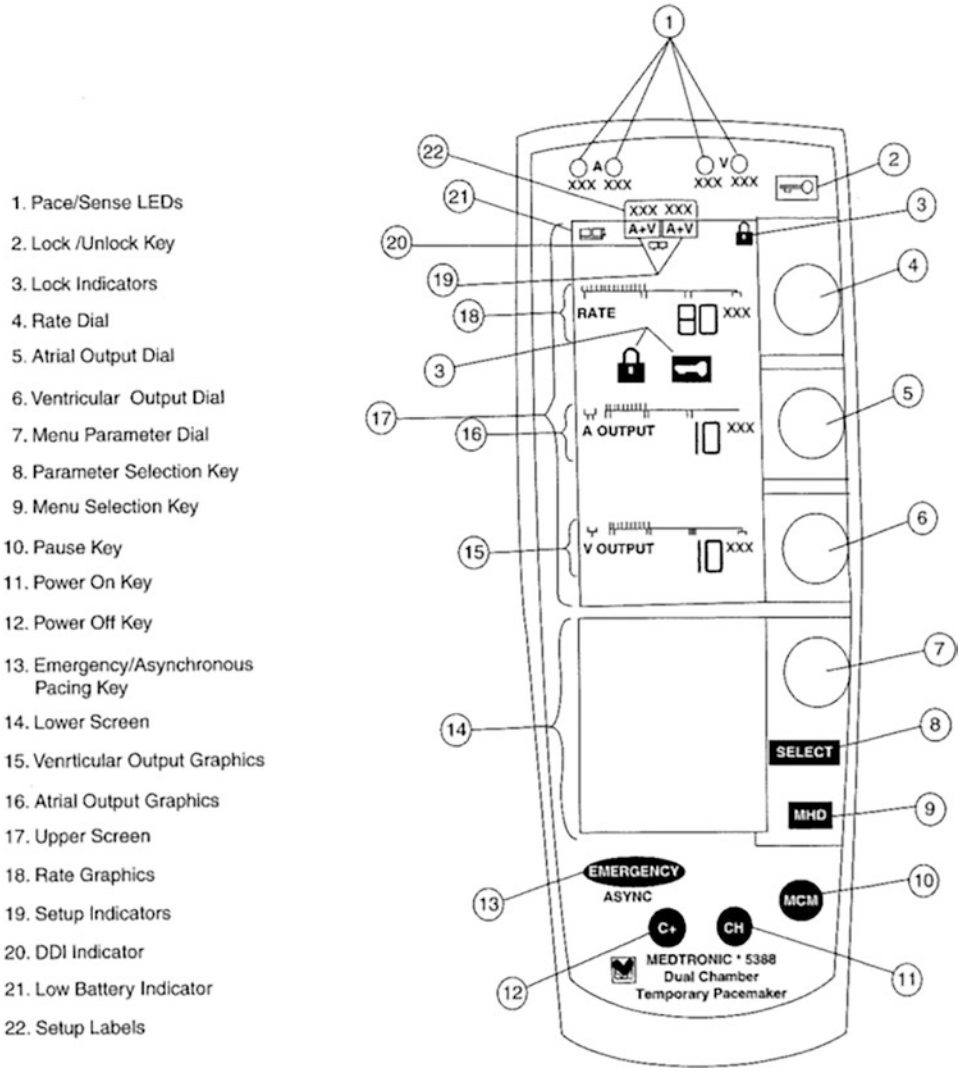


Fig. 21.4 Medtronic 5388 dual chamber temporary pacemaker – pulse generator

chamber temporary pacemaker models. Mode choices for dual chamber temporary pacemakers noted above include: DDD, DDI, DVI, DOO, VVI, VOO, AAI, AOO.

21.4.6 Nomenclature and Parameters to Aid Pacemaker Setting

The different modes of pacing are standardized and described using the North American Society for Pacing and Electrophysiology, and British Pacing and Electrophysiology Group (NASPE/BPEG) devised standard pacemaker codes, the NBG coding system (Table 21.3)

21.4.7 Thresholds

21.4.7.1 Pacing or Capture Threshold

The pacemaker threshold is the minimum amount of energy measured in milliamperes (mA) needed to result in cardiac contraction of the chamber being tested (resulting in an atrial P wave, or ventricular QRS complex). The thresh-

old may vary from beat to beat, and the set output of the pacemaker should be 2–3 times the threshold to provide an adequate safety margin to deliver consistent capture of the heart. Pacing thresholds usually increase significantly over the first 7–10 days and should be checked at least daily in temporary pacemakers.

How to Check the Pacing Threshold?

Pacing threshold is checked by dialing down the output of the chamber being tested. The chamber being tested needs to be set to a rate above the intrinsic rate and actively pacing (otherwise the pacemaker would be inhibited). Testing one lead at a time turn the output to maximum. A pacing spike will be followed by a P wave if the atrium is being paced and capture is present or an R wave if the ventricle is being paced and capture is present. While slowly dialing down the output, note the point at which the pacemaker fails to capture the chamber being tested. Increase the output until capture is achieved. This is the pacing threshold.

Why Should the Pacing Threshold Be Checked?

The pacing threshold is the minimum level of energy measured in mA that produces capture. Over time the pacing threshold is likely to increase secondary to inflammation around the surface of the myocardium where the wire is attached. As noted above, the pacemaker should be set 2–3 times the pacing threshold to allow an adequate margin of safety. It is important to monitor the rate the threshold is increasing as this may be a predictor of impending lead failure. In pacemaker-dependent patients (i.e., patients with inadequate intrinsic rhythm who experience hemodynamic compromise after cessation of pacing), it may be reasonable to check thresholds on a more frequent basis.

21.4.7.2 Sensing Threshold

Sensing threshold is the sensitivity level, measured in millivolts (mV), at which the pacemaker recognizes (senses) an intrinsic cardiac electrical impulse. It is helpful to think of pacemaker sensitivity as the height of a wall that one tries to see over. The higher the number, the higher the wall and the less one sees over its top; therefore, the less the pacemaker senses. The lower the number (the lower the height of the wall), the more one sees over the wall and the more sensitive the pacemaker.

Why Is It Important to Know the Sensitivity Threshold?

If the pacemaker is too sensitive, oversensing can occur. Pacemaker oversensing is when the pacemaker sees electrical activity that it inappropriately recognizes as native cardiac activity and subsequently inappropriately inhibits pacing function. The inappropriate electrical activity may be secondary to muscle tremors, respiratory movement, far-field cardiac electrical activity (sensing intrinsic paced activity from a chamber other than where the pacemaker lead is placed), or environmental electrical interference. If the pacemaker sensitivity is not sensitive enough, undersensing will occur. During undersensing the pacemaker continues to pace at a set rate even when intrinsic cardiac electrical activity is present at a rate faster than the pacemaker is set (i.e., the pacemaker will not inhibit pacing appropriately). This is potentially dangerous during ventricular pacing. If the pacemaker fails to sense the R wave appropriately, and paces on a T wave, it could result in ventricular tachycardia or ventricular fibrillation via an R on T phenomenon. However, in certain emergency situations, such as a patient with symptomatic bradycardia, it may be necessary to accept this risk of ventricular undersensing. An example

is a pacemaker-dependent patient with extra-cardiac electrical interference that produces larger electrical amplitude than the intrinsic cardiac electrical activity. In these situations, the pacemaker could be made totally insensitive (high sensitivity number) and therefore would pace asynchronously.

How to Check Sensitivity Threshold?

The pacemaker rate should be at or below the intrinsic heart rate. Start by turning the sensitivity knob to higher numbers, making the pacemaker less sensitive. Note the point when the pacemaker begins to inappropriately pace. At this point the pacemaker should pace regardless of the intrinsic rhythm. Then begin turning the sensitivity level toward the lowest number (most sensitive setting). Note the point at which the pacemaker senses and is appropriately inhibited. This is the sensitivity threshold.

How to Set Sensitivity Level?

Once the sensitivity threshold is found, the sensitivity level should be set to half or one-third of the threshold.

21.4.8 Intrinsic Rhythm

The underlying intrinsic rhythm can most easily be checked by slowly dialing down the pacemaker rate in VVI mode. The pacemaker should not be stopped abruptly if the patient is in a persistently paced rhythm; doing so may cause a significant period of asystole and discomfort to the patient or loss of consciousness. By dialing the pacemaker rate down slowly, the intrinsic rhythm will slowly resume. When checking the intrinsic rhythm, it is recommended to have the patient lying down. In children, one should not dial down below 50 ppm, and in adolescent or adults, below 40 ppm. Patients may become symptomatic during these checks and experience dizziness, yawning, or nausea prior to loss of consciousness. The temporary atrial and ventricular leads can be connected to a 12-lead ECG machine to record intrinsic atrial or ventricular electrograms.

21.4.8.1 Battery

When a temporary pacemaker is in use, a spare battery should be taped to the pacemaker, making it readily available. The battery should be changed every 24 hours.

21.4.8.2 Documentation

The following is a guideline of the parameters which should be documented each time the pacemaker is checked (at least once a day):

- Pacing threshold
- Sensitivity threshold
- Intrinsic cardiac rhythm
- Pacemaker setting

21.4.9 Contraindications and Precautions

All the new temporary pacemakers are designed to only deliver high rate therapy in AOO mode since rapid ventricular pacing may cause ventricular tachycardia or ventricular fibrillation. High atrial pacing rates may cause unintended

conduction to the ventricles. Thus, defibrillation equipment should be available when delivering high-rate therapy to the atrium. The patient's bed and electrical equipment must be properly grounded because the temporary leads provide a low-resistance circuit through which electrical current can pass through to the heart, causing significant arrhythmias.

21.4.10 Sites and Techniques of Placement

21.4.10.1 Temporary Epicardial (Post-Cardiac Surgery)

Depending on institutional practice, these systems are placed either prophylactically (in operations with high risk of creating heart block) or when AV block develops intraoperatively. Temporary leads are made of stainless steel Teflon-coated wire and are available in unipolar and bipolar forms. The wires are sutured onto the epicardium and brought out through the chest wall. Atrial wires are usually brought out to the right of the sternum, ventricular wires to the left, and are usually clearly labeled. Since they are loosely sutured to the epicardium, these leads should be fixed to the skin to avoid accidental displacement. Patients should be monitored on telemetry while the temporary leads are being used. The exit sites of the wires should be cleaned and dressed daily to avoid infection. In general, pacing thresholds will begin to increase after day 4 from implant, which is thought to be secondary to inflammation at the lead implantation site.

21.4.10.2 Temporary Transvenous

In the pediatric population, transvenous temporary pacing leads are used primarily for adolescents due to the size of the adolescent's vessels and other anatomical considerations. As mentioned, transvenous leads may cause venous congestion or occlusion in small children. In children with single ventricle physiology, who have had a Fontan-type operation, the ventricle would not be accessible via the systemic venous system. In these patients, a transvenous atrial lead is only appropriate if there is no intracardiac right to left shunt and if AV conduction is intact. Temporary transvenous leads are appropriate in older children who develop symptomatic bradycardia with normal cardiac anatomy. There are several types of temporary pacing catheters available. Both unipolar and bipolar leads are available, but more commonly, bipolar leads are used because of improved sensing threshold. There are two major types of catheters, one is more rigid and firm and requires fluoroscopic guidance for catheter placement, and the other type has a balloon tip and can be floated into position. Details about the variety of catheters in each group are beyond the scope of this chapter. These catheters are positioned in the right atrial appendage for atrial pacing or the right ventricular free wall, for ventricular pacing. Depending upon the patient's clinical status and the operator's experience, leads can be placed via different veins. More commonly, the internal jugular or the subclavian approached is used; however, brachial or femoral veins can also be used. After lead placement, a chest radiograph is obtained to document lead position and the catheter is fixed to the skin using non-absorbable suture. Although thresholds tend to rise less rapidly, sensing and pacing thresholds should still be checked daily and the output and sensitivity levels set accordingly. Risks associated with transvenous temporary pacing leads include lead dislodgment and cardiac perforation.

21.4.10.3 Temporary Transesophageal Pacing

This is especially useful in children and can be used to obtain electrograms as well as for pacing. A 4-Fr, 5-Fr, or 10-Fr transesophageal lead can be inserted and advanced until the largest, most distinct atrial electrogram is recorded. It can be used to diagnose the mechanism of atrial arrhythmias, especially if P waves are not obvious on the surface ECG. It can be used to analyze the electrical relationship between the atrium and ventricle. The catheter can be used for overdrive atrial pacing to terminate supraventricular tachycardia. A disadvantage of transesophageal pacing is that large output (usually above 10 mA) and long pulse width (usually 10 ms) are necessary to capture the atrium and may cause patient discomfort. Temporary transesophageal pacing is only capable of atrial pacing; ventricular capture is not possible. The risk associated with transesophageal pacing includes esophageal damage when used for longer periods of pacing with high energy outputs. Transesophageal pacing is generally used for short intervals to terminate supraventricular tachycardia. Atrial pacing during sinus bradycardia with normal AV nodal conduction longer than 24 hours is not routinely recommended.

21.4.10.4 Temporary External Transcutaneous Pacing

Paul Zoll introduced an external cardiac pacemaker system via "pads" more than 50 years ago, often called "Zoll pads." The Zoll Company continues to develop noninvasive temporary pacemakers that may be safe, effective, and well tolerated by patients. This type of pacing may be lifesaving in patients who progress from bradycardia to cardiac arrest as it is designed for easy and rapid application. It may be uncomfortable for patients who are alert and conscious but can be used while a temporary transvenous system is being placed. It is generally not recommended for periods over 24 h.

In an emergency without the availability of an epicardial or a transvenous pacemaker, pacing pads should be applied on the front and back of the chest, and attached to an external pacing device. When turned on, the heart can be paced. Bradycardia that is unresponsive to ventilation, oxygenation, and medication is an indication for emergency transcutaneous pacing; however, pacing is not useful for pulseless electrical activity or asystole.

Emergency transcutaneous pacing is performed using the following steps:

1. Attach pacemaker pads according to manufacturer recommendations. For children less than 15 kg, pediatric pads are recommended, whereas larger children can utilize adult-sized pads. The negative electrode pad is placed over the cardiac apex (typically at the point of maximal impulse), and the positive electrode is placed either in the anterior right subclavicular area or posteriorly between the spine and left scapula.
2. Set the desired rate – usually 100 bpm.
3. In the unconscious patient, begin with a high current output (200 mA) to rapidly achieve capture and then decrease the output to the level needed to maintain capture. Set output 10 mA above the threshold output.
4. In the conscious patient consider sedation and analgesia. Start with a low output and gradually increase the output in 10 mA increments until capture is demonstrated. Set the output 10 mA above the threshold output.
5. It is often impossible to tell from the surface ECG whether the heart is being captured secondary to the large amount of energy-creating artifact that masks the intrinsic electrical signal. Thus, it is important to assess the patient's hemodynamics and palpate a pulse to confirm appropriate pacing capture.

21.4.11 Troubleshooting Pacemaker Malfunction

Failure to pace and failure to capture produce the same outcome – i.e., unable to cause an atrial or ventricular contraction, therefore emergently, actions taken are the same.

Failure to Pace Also known as output failure, which means that the pacemaker fails to deliver an electrical impulse. There will be no pacing spike evident on the ECG. Causes include lead fracture or dislodgement, loose connections, battery failure, generator failure, or oversensing (see below).

Oversensing The pacer perceives noncardiac electrical activity as a true myocardial electrical event and therefore inhibits the pacemaker. These noncardiac stimuli may occur from distant muscle contraction or electromagnetic interference. Although less dangerous than undersensing, oversensing in the DDD mode can lead to an inappropriate inhibition of pacer electrical activity. To reduce oversensing, the pacer must be made less sensitive to artifact electrical activity. This is accomplished by increasing the sensitivity threshold (mV), allowing the pacer to discriminate true myocardial electrical events from the low millivolt artifact.

Failure to Capture Also known as loss of capture, the pacemaker delivers a discharge but the pacing spike is not followed by an appropriate electrical cardiac event (P wave for atrium, QRS for ventricle). Causes include increased pacing threshold, loose connections, prolongation in myocardial refractoriness (long QT), and poor epicardial lead contact (positioning patient on left side may increase contact). The most important cause of loss of capture is a progressive increase in pacing threshold. Over time, the pacing threshold increases which is why the output is initially set at 2–3 times the threshold. This progressive increase is due to inflammation and fibrosis around the surface of the myocardium where the wire is attached. Other factors that increase the threshold are acid-base changes, electrolyte imbalances, antiarrhythmic drugs, myocardial ischemia and hypothyroidism. An increase in the energy output may be required to treat loss of capture pending identification and treatment of causative factors. If loss of capture is noted, output should be immediately increased to maximum output to reestablish consistent pacing, then the pacing threshold should be rechecked. With temporary pacemakers it is imperative to check the pacing threshold regularly (at least daily) to avoid loss of capture.

Failure to Sense (Undersensing) The pacemaker fails to identify the heart's inherent electrical activity and delivers an electrical stimulus inappropriately. With ventricular pacing this is a potentially dangerous situation as an inappropriate electrical impulse may be delivered to the myocardium during an electrically vulnerable period leading to a ventricular arrhythmia (R on T phenomenon). In this situation, the pacemaker is not sensitive enough to detect inherent cardiac electrical activity and therefore needs to be made more sensitive. Increasing the pacemaker sensitivity for inherent cardiac activity is accomplished by decreasing the sensitivity threshold (mV). This allows the pacemaker to "see" cardiac events occurring at a lower millivolt level.

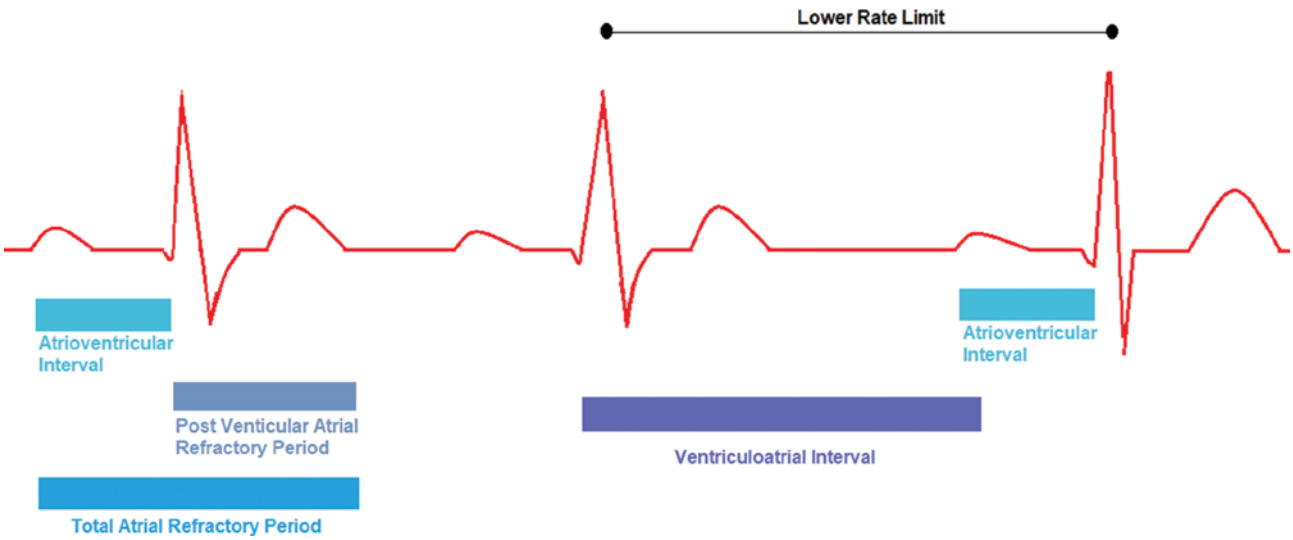


Fig. 21.5 The total atrial refractory period (TARP) is the sum of the atrioventricular interval and the postventricular atrial refractory period (PVARP). The pacer timing cycle in DDD mode takes into account the lower rate limit (LR), an atrioventricular interval, a ventriculoatrial interval, and the post-ventricular atrial refractory period. If intrinsic atrial and ventricular electrical activity is sensed before the LR limit times out, both atrial and ventricular pacer output are inhibited and no pacing occurs. If no atrial activity is sensed before the ventriculoatrial interval is completed, atrial pacing becomes uninhibited and a pacer spike is delivered. If no ventricular activity is sensed before the atrioventricular interval is completed, ventricular pacing becomes uninhibited and a pacer spike is delivered

Temporary pacemakers are often used to treat transient postoperative heart block but may also be used for diagnosing arrhythmias via an atrial electrocardiogram. Surgically acquired heart block persisting beyond 14 days is likely to be permanent

All temporary pacemakers have three major dials: rate (ppm), output (mA), and sensitivity (mV). Dual-chamber models have separate atrial and ventricular output and sensitivity control. Most temporary pacemakers can deliver rapid atrial pacing for overdrive termination of atrial tachyarrhythmias.

Pacing threshold (mA) is the minimum amount of pacemaker output required to capture the heart (a pacemaker spike followed by P or R wave). Output is set at 2–3X the pacing threshold.

Sensing threshold (mv) – minimum amount of intrinsic electric activity that is recognized ("seen") by the pacemaker. Sensitivy is set to one-half to one-third sensitivity threshold.

Alternatively, the pacer may not sense due to lead dislodgement or poor epicardial contact. Placing the patient on their left side may increase the lead and epicardium contact area.

Pacemaker-Mediated Tachycardia (PMT) Depending on intrinsic retrograde AV node conduction, ventricular pacing may result in retrograde ventriculoatrial (V → A) conduction and a subsequent retrograde P wave. With dual chamber sensing and pacing, the pacemaker's atrial lead senses this retrograde P wave and "sees" it as the intrinsic sinus beat, which triggers subsequent ventricular pacing. If this paced ventricular complex again results in a retrograde P wave, a reentrant loop is set up and pacemaker-mediated tachycardia develops. The pacemaker forms the antegrade (A → V) limb of the circuit and the AV node is the retrograde limb (V → A). This potential arrhythmia is best prevented by choosing a post-ventricular atrial refractory period (PVARP) long enough to prevent the sensing of the retrograde P waves. Treatment of PMT typically involves altering the pacemaker programming to make the atrial lead insensitive to the retrograde P wave, or electromagnetic interference. PMT is most easily fixed by prolonging the PVARP. Note that this may affect the upper tracking rate of the pacemaker as this is defined by the total atrial refractory period (TARP), i.e., TARP = AV interval + PVARP (Fig. 21.5). For example, if the AV delay is 170 ms and the PVARP is set to 430 ms, the TARP then is 600 ms, which corresponds to an upper rate of 100/min (rate = 60,000/cycle length in ms). Thus, the pacemaker would not track atrial rates above 100 bpm leading to a 2:1 block for this and higher rates. Other options include programming the pacemaker as DDI, if possible, so as not to track the P waves. If AV conduction is intact, an AAI mode would eliminate PMT by avoiding ventricular pacing.

A suspected pacer malfunction requires rapid support of the child and careful interrogation of the rhythm and pacemaker. Figure 21.6 provides an algorithm to help identify and treat pacemaker malfunctions.

Suspected Pacer Malfunction

↓

Check patient, support ABCs
Call for help

↓

Check ECG for pacer spikes and cardiac electrical complexes

No pacer spike and no subsequent complexes	**Pacer spikes but no subsequent complexes**	**Inappropriately placed pacer spikes (asynchronous pacing)**
↓	↓	↓

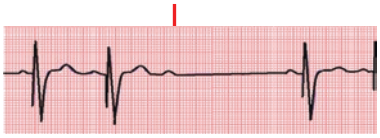
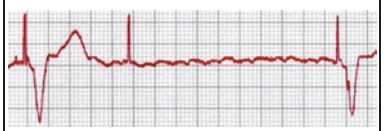
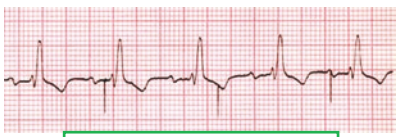
Failure to pace	**Failure to capture**	**Failure to sense**
Causes • Battery or generator failure • Lead dislodgment • Wire fracture • Disconnected wire or cable • **Oversensing** Inappropriate inhibition due too versensing of noncardiac electrical activity Pacer should have fired! 	Causes • Battery or generator failure • Faulty connections • Prolonged QT • Electrolyte abnormalities • **Increased Pacer Threshold** Increases resistance at site of epicardial contact 	Causes • Battery or generator failure • Faulty connections • New BBB • Dysrhythmia • **Undersensing** Inadequate sensitivity causing pacer to miss true cardiac conduction and subsequently delivering inappropriate impulses  Note asynchronous pacing spikes should have fired!
Actions • Assure ABCs • Check power • Check connections • Position patient on left side If **oversensing** suspected (inappropriate inhibition of pacer output), make pacer less sensitive by increasing the mV that the pacer will respond to thus eliminating noncardiac artifact.	Actions • Assure ABCs • Check power • Check connections • Position patient on left side If an increase in the pacer threshold is suspected, increase the delivery of the electrical impulse by turning up the output in mA (20 mA emergently).	Actions • Assure ABCs • Check power • Check connections • Position patient on left side If **undersensing** suspected (pacer missing true cardiac conduction), make pacer more sensitive by decreasing the mV that the pacer will respond to thus allowing pacer to see true cardiac conduction.

Fig. 21.6 Algorithm for suspected pacer malfunction. (Courtesy of Frank A. Maffei)

Undersensing results in overpacing and oversensing results in underpacing.

Pacemaker interrogation, documentation, and battery change should be performed at least once every 24 hours.

Rapid atrial pacing may cause inadvertent rapid ventricular pacing, which can lead to ventricular tachycardia or fibrillation; therefore, a defibrillator machine should be available on standby.

The most important cause of loss of capture is a progressive increase in pacing threshold due to local inflammation and fibrous sheath formation over the electrode tip. Other factors that increase the threshold are acid–base changes, electrolyte imbalances, antiarrhythmic drugs, myocardial ischemia, and hypothyroidism.

Undersensing is characterized by the pacemaker failing to identify the heart's inherent electrical activity and results in the inappropriate delivery of an electrical stimulus. This is a potentially dangerous situation as an inappropriate electrical impulse may be delivered to the ventricular myocardium during an electrically vulnerable period, leading to ventricular arrhythmia (R on T phenomenon)

Review Questions

1. Which of the following is true about epinephrine when used during cardiac arrest?
   (a) At a dose of 0.1 mg/kg epinephrine has mostly beta-adrenergic effects which augment inotropy and chronotropy.
   (b) Epinephrine acts on V1 vascular receptors, leading to vascular smooth muscle vasoconstriction.
   (c) At a dose of 10 mcg/kg epinephrine has mostly alpha-adrenergic effects which supports coronary perfusion.
   (d) Epinephrine acts on beta-2 receptors, leading to vasodilation and decreased cardiac afterload.
   (e) Epinephrine causes cerebral vasodilation, optimizing cerebral perfusion during cardiac arrest.

Correct Answer: C: At a dose of 10 mcg/kg epinephrine has mostly alpha-adrenergic effects which supports coronary perfusion.
Rationale:
The heart is perfused through the coronaries only during diastole; thus, coronary perfusion is dependent on adequate diastolic blood pressure. The predominant hemodynamic effect of epinephrine at standard code dose (0.01 mg/kg or 10 mcg/kg) is manifest through its action at alpha-adrenergic receptors, leading to vasoconstriction and elevation of aortic diastolic blood pressure. Epinephrine also augments inotropy and chronotropy via beta-adrenergic effects; however, these hemodynamic effects are observed at lower doses (usually 1 mcg/kg or less) and are not the primary mechanism by which epinephrine helps during cardiac arrest. Indeed, the beta-adrenergic effects may cause adverse effects when epinephrine is used in cardiac arrest since they increase myocardial oxygen demand. Vasopressin acts on V1 vascular receptors, also causing vasoconstriction that increases coronary perfusion pressure; while low-dose vasopressin causes vasodilation of the cerebral circulation. However, there is insufficient evidence to make a recommendation for or against the routine use of vasopressin during pediatric cardiac arrest.

2. Which of the following is a marker of quality CPR?
   (a) Providing chest compressions at a rate of 80–100 per minute.
   (b) Giving ventilations via an advanced airway at a rate of 20 per minute.
   (c) Ensuring compressions at a depth of one-fourth the chest diameter.
   (d) Lifting the palm to allow full recoil between chest compressions.
   (e) Performing regular pulse and rhythm checks every minute.

Correct Answer: D: Lifting the palm to allow full recoil between chest compressions
Rationale:
The five components of high-quality CPR are (1) ensuring chest compressions at an adequate rate of 100–120 per minute, (2) depth of at least one-third the anterior-posterior diameter of the chest, (3) allowing full recoil between compressions, (4) minimizing interruptions in chest compressions, and (5) avoiding excessive ventilation. Ensuring regular switches (approximately every 2 min) in chest compressors is recommended to decrease fatigue-associated leaning during CPR; however, performing pulse and rhythm checks every minute would lead to frequent interruptions in chest compressions that could be deleterious.

3. A previously healthy 1-year-old girl presented 2 weeks ago with tachypnea, tachycardia, and hepatomegaly. On initial chest radiograph she had cardiomegaly with evidence of pulmonary edema. An echocardiogram demonstrated a structurally normal heart with left atrial and left ventricular

(LV) dilation, and moderately depressed LV systolic function. After admission to the intensive care unit, her clinical status rapidly declined, leading to intubation and initiation of vasoactive support. As her hemodynamics continued to worsen over the next 2 days, the decision was made to initiate veno-arterial extracorporeal membrane oxygenation (ECMO) support. After several days of full ECMO support, her lung disease improved, renal function normalized, and her neurologic examination remained reassuring. However, she failed several attempts to wean ECMO support over the following week with persistent LV dilation and severe myocardial dysfunction. An endomyocardial biopsy was obtained and revealed myocyte hypertrophy and degeneration, with areas of fibrosis and no evidence of lymphocytic myocarditis. The cardiology team is now considering listing her for cardiac transplantation.

Of the following, the BEST choice for ongoing mechanical circulatory support in this patient is:

(a) Initiate intra-aortic balloon pump support.
(b) Remain on current extracorporeal membrane oxygenation support.
(c) Transition to a continuous axial flow ventricular assist device.
(d) Transition to a continuous centrifugal ventricular assist device.
(e) Transition to a pulsatile ventricular assist device.

Correct Answer: E: Transition to a pulsatile ventricular assist device since this is the only FDA approved VAD device for children and some data suggests that pulsatile flow better preserves the microvasculature.

4. A 13 kg 3-year-old patient with severe pediatric acute respiratory distress syndrome on VV ECMO develops desaturation and elevated venous drainage saturation. The patient's ECMO flow is 1.6 LPM (approximately 3.2 L/min/m^2). You suspect the patient has developed recirculation.

   Of the following, the BEST choice for correcting recirculation in this patient is:

   (a) Change the oxygenator.
   (b) Increase the ECMO flow to improve systemic oxygenation.
   (c) Reposition the cannula so that the oxygenated venous return to the patient is directed towards the tricuspid valve.
   (d) Decrease the ECMO flow rate.
   (e) Consider transition to VA ECMO.

Correct Answer: D: Decrease the ECMO flow rate

5. A 4-year-old patient with heterotaxy and L-looped ventricles (L-TGA) is post-op following a sub-aortic muscle resection to relieve left ventricular outflow tract obstruction. After surgery the patient was in complete heart block and paced using temporary atrial and ventricular pacing wires placed at the end of surgery. On post-op day 15 the patient continues in complete heart block with ongoing atrially sensed and ventricular pacing. Over the last 3 days the ventricular lead capture threshold steadily increased and is now noted to be 6 mA. The output was adjusted to 18 mA.

   What is the next best step?

   (a) Decrease the sensitivity.
   (b) Speak to the cardiothoracic surgeon regarding epicardial dual-chamber permanent pacemaker implantation.
   (c) Adjust the AV delay and PVARP to allow for the pacemaker to be set at a higher heart rate.
   (d) Check the pacemaker function every 12 h instead of every 24 h.
   (e) Decrease the output to a 2x safety margin.

Correct Answer: B: Speak to the cardiothoracic surgeon regarding epicardial dual-chamber permanent pacemaker implantation

6. A 6-month-old patient is post-op day 2 following repair of a complete AV canal, the patient has been atrially sensed and ventricularly paced for transient postoperative complete heart block. There is intermittent return of AV nodal conduction on the most recent pacemaker interrogation. During morning rounds the patient is noted to be tachycardic with an atrially sensed ventricularly paced rhythm. Pacemaker-mediated tachycardia is suspected and confirmed by switching the pacing mode to VVI. The underlying rhythm continues to show complete heart block.
   In this situation what is the best way to prevent further episodes of pacemaker mediated tachycardia?
   (a) Increase the post-ventricular atrial refractory period (PVARP).
   (b) Increase the sensitivity on the ventricular lead.
   (c) Decrease the output on the atrial lead.
   (d) Switch the pacing mode to AAI.
   (e) Increase the rate setting of the pacemaker.

Correct Answer: A: Increase the post ventricular atrial refractory period (PVARP).

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Central and Peripheral Nervous System

Contents

Central and Peripheral Nervous Systems: Development, Structure, and Function

Daniel J. Rogers, Kiran M. Sargar, and Frank A. Maffei

Contents

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Learning Objectives

- Review the embryologic development of the central and peripheral nervous system.
- Understand the structure–function relationships within the central nervous system.
- Review the development of the blood supply to the central nervous system.
- Recognize the elements comprising the blood brain barrier.
- Review the development of the blood brain barrier.
- Identify the major arteries and their branches supplying blood flow to the brain and spinal cord.
- Understand the principle of cerebral autoregulation and the elements by which it is modulated.
- Identify the components of the cerebral ventricular system.
- Review the composition, synthesis, and flow of cerebrospinal fluid within the ventricular system.
- Identify the three primary meningeal layers and their function.
- Understand the key elements of the peripheral nervous system and their function.

22.1 Introduction

Participating in the care of critically ill children requires an astute knowledge of the central and peripheral nervous systems. In responding to injury and dysfunction of the nervous system, it is necessary to understand the development, structure, and function of the nervous systems. This chapter will describe the development, structure, and function of the central and peripheral nervous systems within the context of caring for the critically ill child.

22.2 Development of the Nervous System

The nervous system is derived from three primary sources, all of which originate from the early ectoderm of embryogenesis. A subset of ectodermal cells differentiates into the neural ectoderm, which gives rise to the *(1) neural plate, (2) neural crest cells, and (3) ectodermal placodes* (Fig. 22.1). The *neural plate* will ultimately give rise to the central nervous system (CNS), somatic motor neurons, and preganglionic autonomic neurons. *Neural crest cells* differentiate and migrate prior to the fusion of the neural tube to give rise to glial cells and neurons of the peripheral nervous system (PNS), somatic and auto-

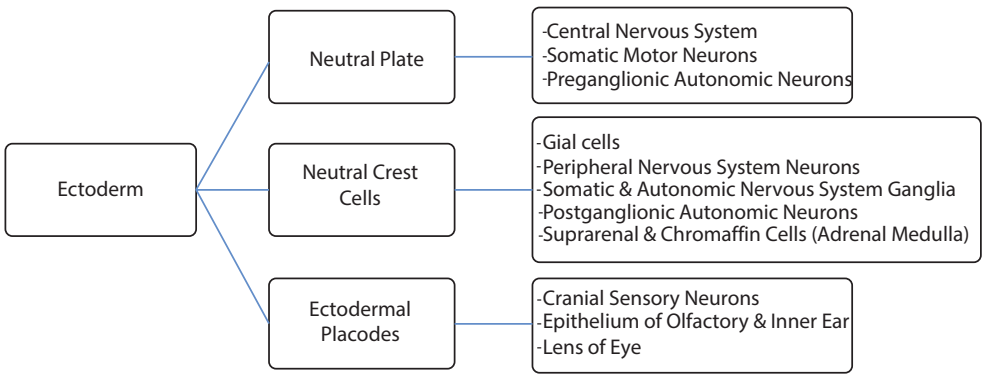


Fig. 22.1 Embryologic development of the nervous system

nomic nervous system ganglia, postganglionic autonomic neurons, and suprarenal and chromaffin cells found within the adrenal medulla. The *ectodermal placodes* are thickenings of the neural ectoderm in the region of the embryonic head from which the cranial sensory neurons, the epithelium of the olfactory and inner ear, and the lens of the eye develop.

Several key developmental processes occur both sequentially and in parallel and are modulated by a variety of molecular, physiologic, and functional pathways. These processes begin in the early fetus and continue through early childhood and into adolescence.

22.2.1 CNS Development

Neurogenesis, neuronal migration, and neuronal differentiation continue through the 25th week of gestation, when processes such as arborization, synaptogenesis, and programmed cell death begin. The embryonic central nervous system is vulnerable to external and internal stressors during this time.

Under the direction of the mesodermal notochord, the neural plate establishes itself from ectodermal tissue within the first 2–3 weeks of fetal development. *Neurogenesis*, which includes the proliferation, growth, and development of neuronal tissue, occurs throughout this process. Neuronal precursor cells establish their position along the embryonic axis, where they will either continue to proliferate or cease proliferation and become post-mitotic cells. Precursor cells can become neuronal cells or glial (supportive) cells at that point. It is important to emphasize how vulnerable the developing brain is to external and internal stressors, such as alcohol exposure and the incidence of fetal alcohol syndrome. The early brain regions, consisting of the *prosencephalon* (forebrain), *mesencephalon* (midbrain), and *rhombencephalon* (hindbrain), begin to appear during the first month of fetal life.

These early brain regions eventually produce the following structures of the brain:

- *Prosencephalon*: Cerebral hemispheres, olfactory cortex, hippocampus, basal ganglia, thalamus and the caudal portions of the hypothalamus, lateral and third ventricle, optic nerve, and mammillary bodies.
- *Mesencephalon*: Cerebral aqueduct, cerebral peduncles, tegmentum, tectum, red nucleus, substantia nigra, and crus cerebelli.
- *Rhombencephalon* (*from rostral to caudal*):
  - *Isthmus rhombencephali:* Superior medullary velum and superior cerebellar peduncles.
  - *Metencephalon*: Middle cerebellar peduncles, middle portion of fourth ventricle, cerebellum, and pons.
  - *Myelencephalon*: Inferior cerebellar peduncles, caudal portion of the fourth ventricle, and the medulla oblongata.

Brain growth begins early in gestation and proceeds rapidly through the first few postnatal years. Hemispheres begin to take shape during weeks 5–10 of fetal development. Fetal twitches and extremity movement occur during this timeframe. Driven by a variety of growth factor cascades and signaling pathways, rapid cell division occurs producing up to 200,000 new neuronal cells every minute. In parallel to cellular proliferation, neuronal cells continue to develop and grow by replicating organelles, molecules, and other intracellular components.

Between the 12th and 24th week, neuronal migration begins to occur under the direction of neurotransmitters, such as glutamate and various neurotrophins. Deeper layers of the cortex develop first followed by more superficial layers. Neuronal cells migrate outward under the guidance of a subgroup of progenitor glial cells referred to as *radial glia*. By the 13th week of gestation, cortical layers are established.

Lissencephaly occurs because of abnormal neuronal migration, resulting in the absence of normal cortical folds.

Lissencephaly, which translates as "smooth brain" because of the appearance of the cortex in the absence of normal cortical folds, is a consequence of genetic and/or environmental stressors impeding normal neuronal migration during this time. Although phenotypic variability exists, many of these children exhibit features such as microcephaly, abnormal facial features, failure to thrive, spasticity, seizures, and severe developmental delay. When these process alterations continue, delay in achieving the milestones of fetal development such as head movement, chest movement, jaw opening, sucking, swallowing, walking movements, pain reactions, and sleep cycles becomes evident.

Neurogenesis, neuronal migration, and neuronal differentiation continue through the 25th week of gestation, when processes such as *arborization*, *synaptogenesis*, and *programmed cell death* begin. All neuronal cells begin as stem cells and progress through the progenitor cell, post-mitotic cell, precursor cell, and the neuronal cell state. Genetic factors that determine neuronal and glial cell lineages also determine differentiation of neuronal cells exhibiting various sizes, shapes, neurotransmitters, receptors, and neurotrophic factors.

Failure or errors in neuronal differentiation or fusion of the neural tube results in a variety of conditions such as:

- *Craniorachischisis*: The entire length of the neural tube fails to fuse, thus exposing the whole central nervous system.
- *Cranioschisis* or anencephaly: The neural tube fuses to form the spinal cord, but does not fuse correctly to form the brain, resulting in exposed or absent cerebral hemispheres.
- *Spina bifida occulta*: Failure of one or more vertebral arch fusion with spinal cord and meninges occupying their normal location.
- *Spina bifida cystica*: Failure of vertebral arch fusion with protrusion of a cystic structure containing meninges and cerebrospinal fluid (i.e., *meningocele*) or meninges, spinal cord, nerve roots, and cerebral spinal fluid (i.e., *meningomyelocele*). The latter presents with significant neurological deficits (bowel and bladder incontinence, paralysis, loss of sensation, and hip and lower extremity malformation) in approximately 99% of cases (Fig. 22.2).

Synaptogenesis and the primitive connectivity of the fetal central nervous system begins as early as 6 weeks gestation but becomes more active during the 17th and 18th week of fetal development. This early phase of synaptogenesis is guided predominantly by the genetic blueprint, but subsequently develops at a rapid pace and becomes more influenced by environmental stimuli and experiences. This later process is extremely active in infants and young children, which may account for the resiliency displayed by this age group in response to injury. Synaptogenesis continues into adolescence and adulthood, although a significant amount of synaptic loss also occurs at this stage of development.

At birth, neurogenesis and neuronal migration are complete, while synaptogenesis, arborization, and axonal growth continue at a substantial rate until around 2 years of age. The number of synapses in a 2-year-old is significantly greater than that of an adult. This difference exists because of *synaptic pruning*, which occurs from about age 2 until adolescence and even adulthood. Synaptic pruning, much like synaptogenesis, is under the control of genetic and environmental influences. These processes manifest in the behavioral milestones witnessed during early and late childhood. Aberrations in synaptic development result in a variety of clinical syndromes.

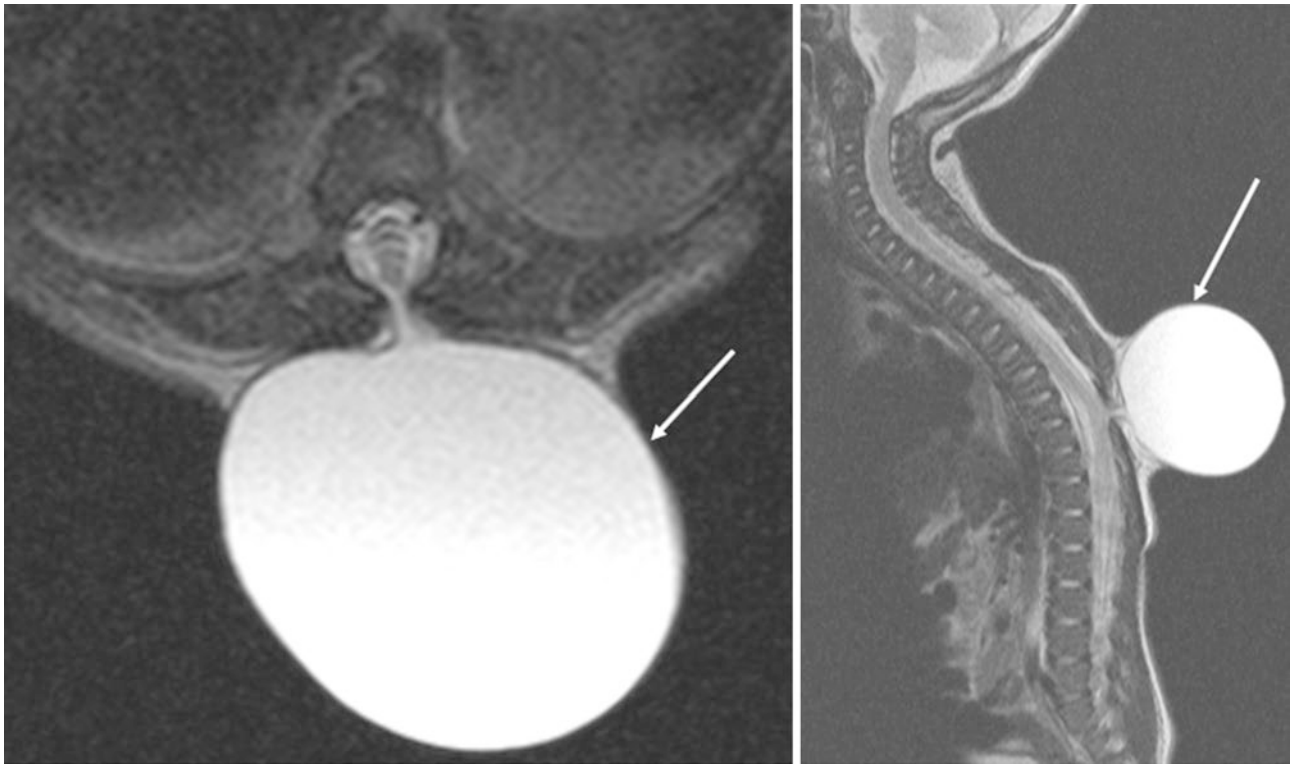


Fig. 22.2 Axial and sagittal T2-weighted images of the thoracic spine in this one-day-old girl demonstrate spina bifida with thoracic meningocele (arrows). Notice the widening of the posterior elements of the thoracic vertebra at this level with the communication of meningocele with the CSF in the spinal canal

Fragile X syndrome is the most common inherited form of developmental disability occurring in both males and females, although symptoms in the latter are milder. Fragile X syndrome is the consequence of a mutation on the FMR1 gene of the X chromosome. The outcome of this is an overproduction and impaired pruning of neuronal synapses. Features of patients with Fragile X syndrome include cognitive disability, long and narrow faces, large ears, flexible fingers, and large testicles. A large percentage also display features of autism, delayed speech, attention deficit disorder, hyperactivity, and seizures.

The number and type of neuronal cells are tightly regulated during both prenatal and postnatal CNS development through the process of programmed cell death (PCD) or apoptosis. This can occur in one of two ways. Apoptosis transpires in post-mitotic and neuronal precursor cells exposed to absent, abnormal, or premature differentiation signals, thus preventing abnormal neurogenesis. Apoptosis can also occur in neuronal cells that fail to make synaptic connections. Failure or irregularities in programmed cell death due to genetic or environmental factors result in a range of phenotypic outcomes including neurodegenerative diseases, malignancies, and various developmental anomalies.

Myelin is a lipid-rich substance found in the central and peripheral nervous system which insulates axons to ensure rapid propagation of action potentials. *Myelination* or the process of producing myelin and encasing adjacent axons begins to occur 1–2 months prior to birth, continues into the 3rd decade of life, and parallels the maturation of cognitive function demonstrated during this period. *Oligodendrocytes* and *Schwann cells* are responsible for myelination in CNS and PNS, respectively. Each oligodendrocyte is typically responsible for

Fragile X syndrome, the most common inherited form of developmental disability, occurs as a consequence of a mutation in the FMR1 gene of the X chromosome, resulting in errors in synaptic pruning.

Programmed cell death prevents abnormal neurogenesis and synaptogenesis and occurs under the direction of both genetic and environmental triggers.

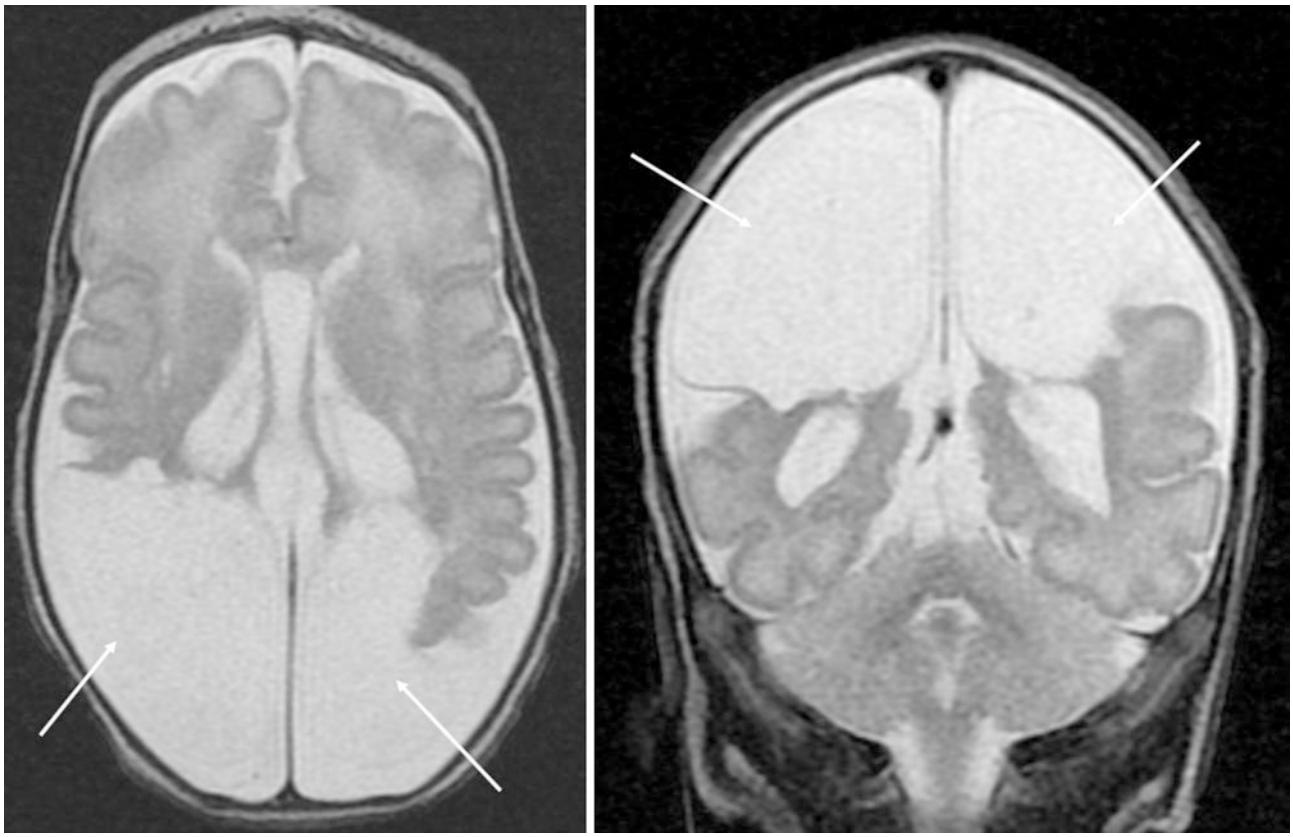


Fig. 22.3 Periventricular leukomalacia in this 30-day-old girl with EGA of 27 weeks. Axial and coronal T2-weighted images show cystic encephalomalacia involving bilateral parieto-occipital lobes (arrows)

Myelination or the process of producing myelin and encasing adjacent axons begins to occur 1–2 months prior to birth and continues into the 3rd decade of life.

the myelination of up to 10–15 axons, while a Schwann cell is responsible for the myelination of a single axon. Preoligodendrocytes initiate myelination and are extremely sensitive to insults such as hypoxia or inflammation.

Disruption of normal myelination in the central nervous system may result in *periventricular leukomalacia (PVL)* or white matter lesions secondary to necrosis, scaring, and cyst formation in areas adjacent to the lateral ventricles of the brain (Fig. 22.3). Children with PVL exhibit a range of clinical symptoms including developmental delay, quadriparesis, cerebral palsy, and seizures.

22.2.2 Glial Cells

Glial cells are the most numerous cell type in the CNS and serve a vital role in supporting neuronal function and CNS integrity. Various types of glial cells exist and can be classified into two primary categories: *macroglia* and *microglia*.

Macroglial cells include astrocytes, radial glial cells, oligodendrocytes (CNS), and Schwann cells (PNS). Radial glial cells, oligodendrocytes (CNS), and Schwann cells (PNS) were described previously regarding their role in neuronal migration and myelination respectively. Astrocytes do not appear until after neuronal migration and differentiation but are the most populous of the glial cells and have several roles. Astrocytes assist in maintaining the homeostatic milieu of the brain parenchyma and are an important contributor to both synaptogenesis and the establishment of the blood brain barrier.

Astrocytes maintain concentrations of calcium (Ca^{2+}) and hydrogen (H^+), help scavenge free radicals, detoxify compounds such as ammonia, participate in the immune response, produce growth factors, and modulate synaptic neurotransmitter concentrations. At the synapse, astrocytes are a member of a 3-part structure, which includes the presynaptic and postsynaptic neurons and function to maintain ion and neurotransmitter concentration. Astrocytes project foot processes along the endothelial layer of the blood brain barrier and contribute to the formation of tight junctions. In the setting of hypoxic, metabolic, or traumatic insult to the CNS, astrocytes take up excess glutamate and potassium (K^+) and regulate the concentration of hydrogen (H^+) through energy-dependent processes, which establishes a sodium (Na^+) gradient utilized for transport. The consequence of this is astrocyte swelling, which, if significant, can impair synaptic function and cerebral blood flow.

Microglial cells originate from the myeloid cell lineage and are the predominant phagocytic cell in the CNS, although they represent only approximately 10% of the CNS cell population. At baseline they exist in a dormant state until activated by injury such as infection, inflammation, or traumatic insult. It is not entirely clear whether their function is characterized as neurotoxic, neuroprotective, or a balance between the two roles. It is known that activated microglial cells play a role in Alzheimer disease and prion disease, and therapeutic strategies are currently in development focusing on modulation of microglial activation and function.

22.2.3 Development of CNS Vasculature and Blood Brain Barrier

The vascular supply to the brain can be divided into the anterior circulation, arising from the paired internal carotid arteries, and the posterior circulation, arising from the paired vertebral arteries (Figs. 22.23, 22.25, and 22.26). The vascular supply to the spinal cord consists of the interconnected longitudinal and segmental systems that arise from the vertebral arteries and the aorta.

The vascular system is one of the first systems to develop in the maturing fetus. *Vascular plexi* can be found along the primitive neural tube and grow in a radial pattern from the outer to the deeper inner structures. This occurs through three phases of development:

- *Vasculogenesis*: Development of new blood vessels from differentiated endothelial (i.e., mesodermal) cells
- *Angiogenesis*: Development of new blood vessels from existing blood vessels
- *Development of the blood brain barrier*

Tissue oxygen level plays a critical role such that a low level triggers angiogenesis, whereas a high level has an inhibitory effect. Individuals with chronic hypoxia (e.g., cyanotic heart disease) have increased capillary density, which remodels and can be restored to normal once oxygenation is reestablished.

The development of the blood brain barrier occurs with early vascularization. Immunologic markers for vascular tight junctions can be found as early as 14 weeks gestation. The immature blood brain barrier, which is often characterized as leaky, is highly developed and possesses some attributes not seen in the mature blood brain barrier. In general, the fetal blood brain barrier has permeability to large macromolecules that is comparable to the mature blood brain barrier but is relatively more permeable to smaller molecules.

The mature blood brain barrier consists of cellular and non-cellular components, which include:

- *Endothelial cells* linked together by tight junctions, which prevent paracellular diffusion. The endothelial layer is devoid of fenestrations and is highly selective, limiting transcellular diffusion to select water-soluble substances. The high electrical resistance of the endothelial layer makes it impermeable to even small ions such as sodium and potassium.
- *Pericytes* surround the endothelial cells, provide support to the endothelium, participate in phagocytosis, and have contractile properties, which helps regulate blood vessel reactivity.
- *Basement membrane* surrounds the capillaries and small drainage venules. Around the small drainage venules, the basement membrane consists of an endothelial layer, the meningeal epithelium, and a parenchymal layer.
- *Perivascular astrocyte end feet* are extensions of the surrounding astrocytes that envelop pericytes and regulate the flow of a variety of substances across the blood brain barrier through specific transporters and intracellular metabolic pathways.
- *Extracellular matrix* surrounds the cellular components of the blood brain barrier, although its role is not clearly understood with regard to sustaining the blood brain barrier.

The blood brain barrier is composed of an endothelial cell layer, pericytes, basement membrane, perivascular astrocytes, and the extracellular matrix.

The blood brain barrier consists of three barriers: *(1) the blood brain barrier, (2) the blood CSF barrier, and (3) the CSF brain barrier*. All three barriers are important in maintaining the ionic and biochemical milieu that is important for supporting neurologic function. The blood brain barrier is impermeable to hydrophilic ions, molecules, and proteins and permeable to lipophilic molecules such as carbon dioxide (CO_2), oxygen (O_2), and ethanol. Essential molecules, such as glucose and amino acids, are transported by carrier proteins *GLUT1* and *L1*. In addition to functioning as a barrier and facilitator of essential molecule transport, the blood brain barrier is capable of removing a variety of drugs and hydrophobic molecules and participates in the metabolism of circulating catecholamines (e.g., monoamine oxidase).

Because the blood brain barrier is impermeable to hydrophilic substances, it prevents movement of cations (e.g., potassium, sodium) and osmolar agents, which is a feature targeted by hyperosmolar therapies (e.g., mannitol, hypertonic saline) to treat intracerebral edema and prevent intracranial hypertension by drawing water out into the vascular space. Lipophilic substances such as benzodiazepines, nicotine, and heroin are rapidly taken up into the CSF and thus the concentration of lipophilic substances in the CSF often mirrors that of the plasma. Lipophilic substances that are highly protein bound (e.g., phenytoin) are an exception to this rule, which is why the free level of phenytoin is more indicative of the CSF concentration.

22.3 Structure and Functions of the Nervous System

Although the precise developmental timeline is variable, the pattern and order of development of the nervous system has remained relatively conserved across a variety of species, which allows the use of animal models to make inferences about human development. Accordingly, the configuration of the human nervous system has also remained relatively conserved along its evolutionary axis.

The major components of the nervous system are classified by both anatomical and physiological characteristics. Typically, the nervous system is divided into the central nervous system (CNS) and peripheral nervous system (PNS) (Fig. 22.4).

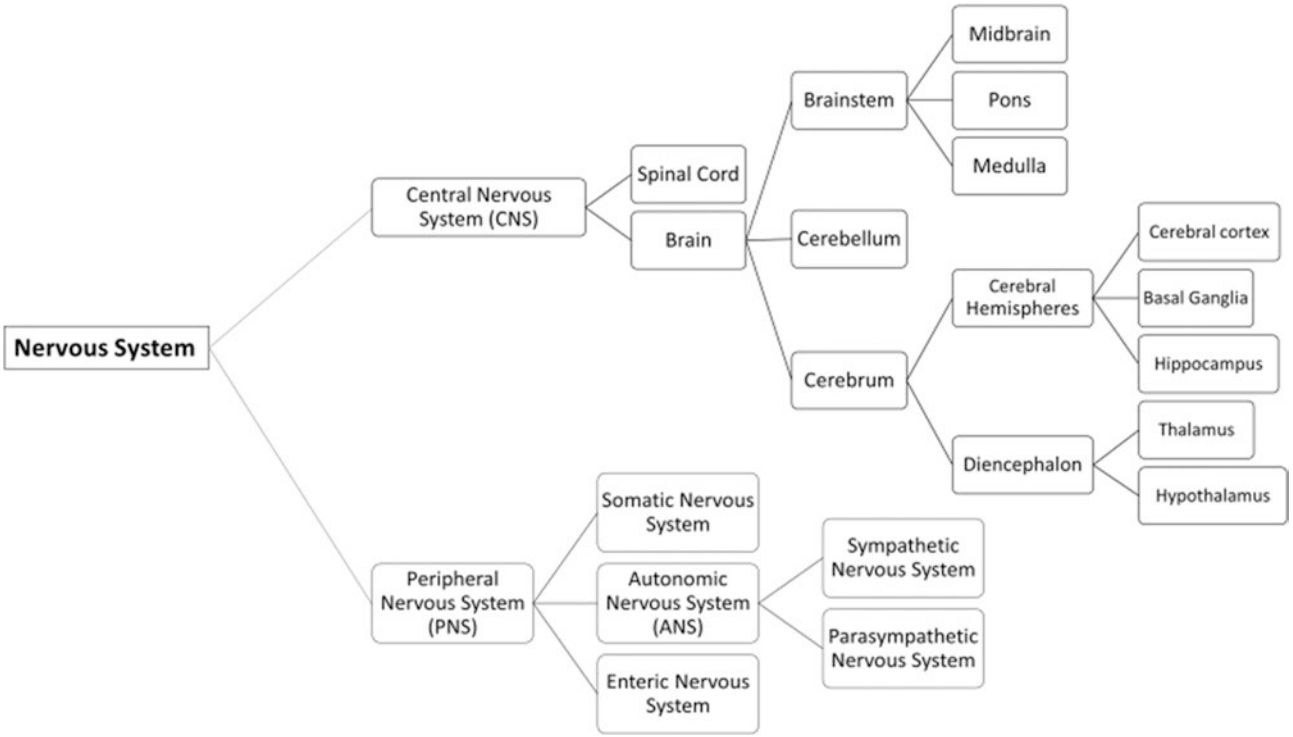


Fig. 22.4 Central and peripheral nervous system

22.3.1 Central Nervous System: Spinal Cord

The spinal cord begins to develop in the 3rd week of gestation with the formation of the neural tube. It extends from the brainstem to the lumbar region of the vertebral column and consists of afferent and efferent pathways conducting signals to and from the sensory and motor cortices, thus coordinating reflexes and providing an interface for communication between the brain and peripheral nervous system.

After the 12th week of gestation, the vertebral column grows in length at a rate more rapid than that of the spinal cord. Consequently, the spinal cord ends more rostrally (at a higher level) relative to the vertebral column. At birth, the spinal cord terminates around L3 (Fig. 22.5), and because this pattern of growth persists, the spinal cord eventually ends around L1-L2 by adulthood (Fig. 22.6). Clinically, this is significant when identifying the appropriate level for lumbar puncture, which is L3–L5 in infants and L2–L5 in adolescents and adults. The spinal cord in neonates extends further down the spinal canal than in adults and older children. The interspace between L4 and L5 is the preferred initial site for the lumbar puncture in a neonate.

Beyond the 12th week of gestation, the spinal cord grows more slowly than the vertebral column. Consequently, the infant spinal cord terminates at the level of L3, thus allowing a lumbar puncture to be performed safely below this level.

Structurally, the spinal cord is divided into 31 segments: 8 cervical (C1–C8), 12 thoracic (T1–T12), 5 lumbar (L1–L5), 5 sacral (S1–S5), and 1 coccygeal. Of note, the nerve exits above the corresponding vertebral level in the cervical region except for C8, which exits above T1. In the remainder of the spinal cord, the nerve exits below the corresponding spinal level. Functionally, lesions to the spinal cord result in either sensory deficits with injury to the ascending pathways and/or motor deficits due to interruptions in the descending pathways. Complete transection results in spinal shock (i.e., flaccid paralysis and loss of deep tendon reflexes) and later evolves to manifest as spastic paralysis and hyperactive deep tendon reflexes due to the disruption of inhibitory pathways from motor centers in the cortex.

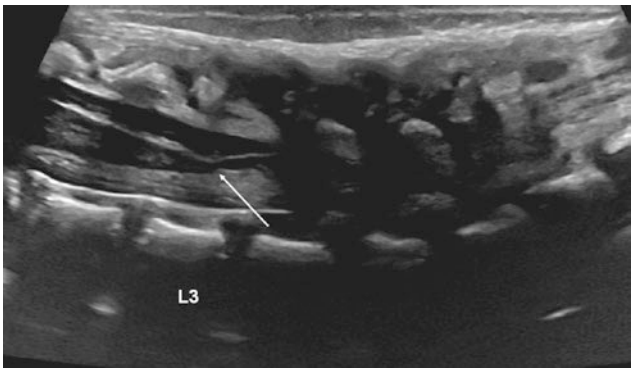


Fig. 22.5 Longitudinal gray-scale ultrasonography image of the lumbar spine in a one-day-old boy showing conus medullaris terminating at L3 level (arrow)

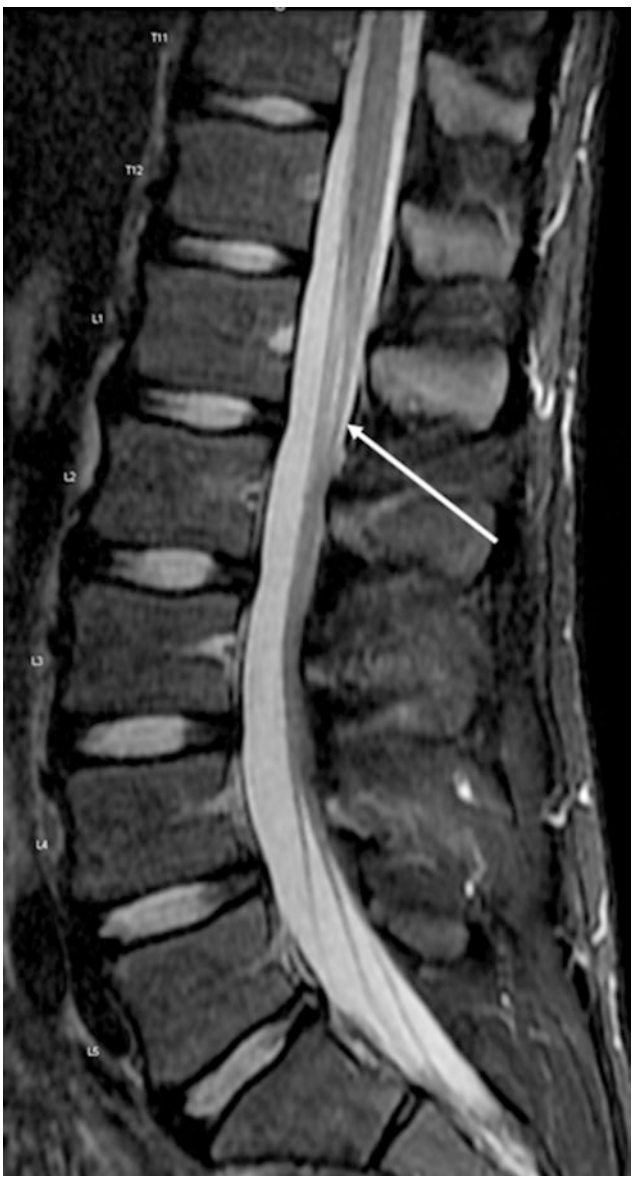


Fig. 22.6 Sagittal STIR-weighted image of the lumbar spine in a 15-year-old boy showing conus medullaris at L1–L2 level (arrow)

22.3.2 Central Nervous System: Brain

22.3.2.1 Brainstem

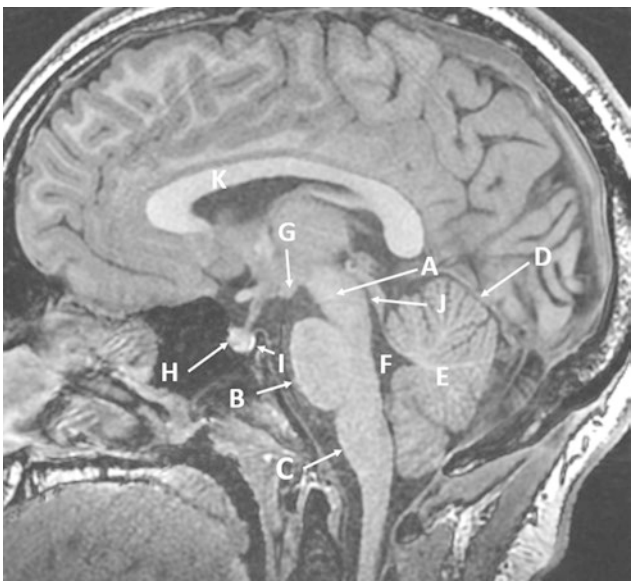
The brainstem is the location for the nuclei of cranial nerves III–XII, and it also serves as a relay station for various ascending, descending, and cerebellar tracts.

The brainstem extends cranially from the spinal cord and serves a variety of vital functions. The central canal of the spinal cord enlarges into the fourth ventricle, which is situated in the brainstem. The brainstem is the location of several ascending and descending pathways, all the cranial nerve nuclei (except for cranial nerves I and II) and some sensory nuclei. Descending pathways (e.g., corticospinal tract) and ascending pathways (e.g., spinothalamic tract) traverse the brainstem, while a few tracts synapse, end, or arise in the brainstem. In addition to serving as a relay station for the various ascending and descending tracts, pathways directed toward and away from the cerebellum also travel through the brainstem via the cerebellar peduncles (i.e., superior, inferior and middle). Because of its many vital roles, including control of the respiratory and cardiovascular systems and arousal, injury or insult to the brainstem or adjacent regions often results in significant neurologic compromise. The brainstem is composed of three primary segments, the medulla or medulla oblongata, pons, and midbrain (◘ Fig. 22.7).

22.3.2.2 Medulla

Cranial nerves IX (glossopharyngeal), X (vagus), XI (accessory), and XII (hypoglossal) emerge from the medulla.

The medulla (◘ Figs. 22.7 and 22.8) extends cranially from the spinal cord and lies anteriorly and inferiorly to the cerebellum. The *glossopharyngeal* (CN IX), *vagus* (CN X), *accessory* (CN XI), and *hypoglossal* (CN XII) cranial nerves emerge from the medulla. Ascending sensory pathways of the *dorsal column* (fine touch and proprioception of the lower and upper body) synapse on the *nuclei gracilis* (lower body) and *nuclei cutaneous* (upper body) cross to the contralateral side and ascend to the thalamus as the fibrous medial lemniscus. The *spinothalamic tract* (touch, pain, and temperature) crosses at the level of the spinal cord and ascends anterolaterally to the medulla en route to the thalamus. The *spinoreticular tract* (pain), like the spinothalamic tract, syn-



◘ **Fig. 22.7** Sagittal T1-weighted image of the brain showing various anatomical structures. Midbrain (A). Pons (B). Medulla (C). Tentorium cerebelli (D). Cerebellum (E). Fourth ventricle (F). Mammillary body of hypothalamus (G). Anterior pituitary gland (H). Posterior pituitary gland (I). Aqueduct of sylvius (J). Corpus callosum (K)

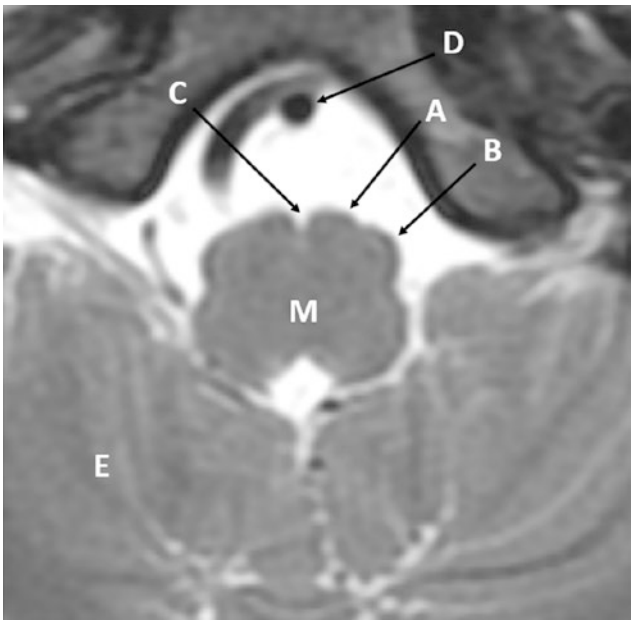


Fig. 22.8 Axial T2-weighted image of the infratentorial compartment showing medulla (M). Medullary pyramid (A). Medullary olive (B). Ventral median fissure (C). Basilar artery (D). Cerebellum (E)

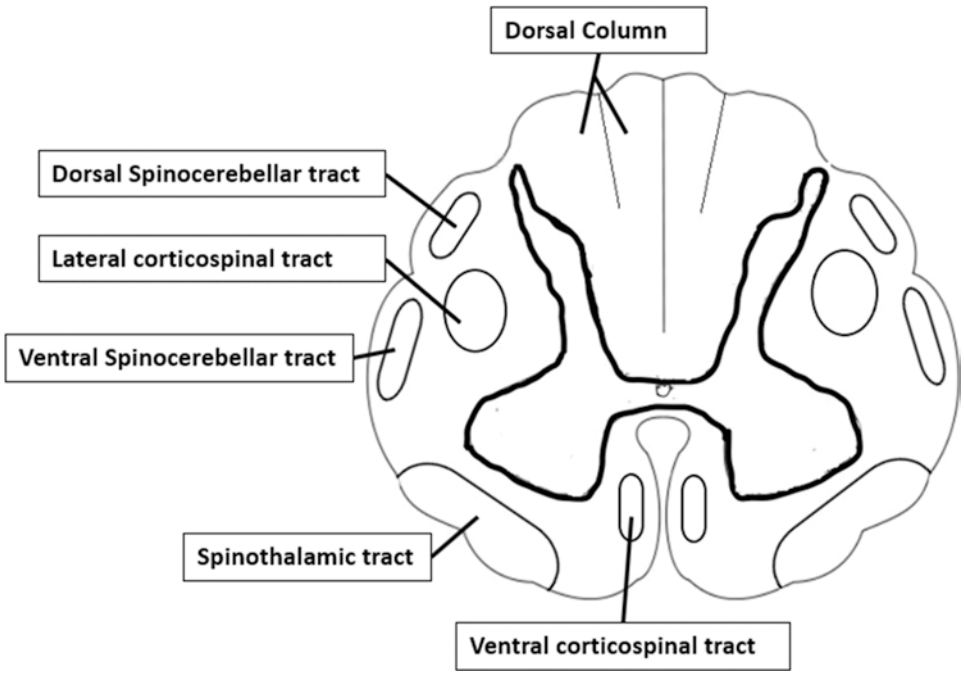


Fig. 22.9 Spinal cord tracts

apses and crosses at the level of the spinal cord and ascends through the medulla. The *ventral and dorsal spinocerebellar tracts* pass through the medulla to the cerebellum to provide proprioceptive information. The descending corticospinal tract (motor) descends from the motor cortex and crosses over in the medulla before traveling anteriorly in the spinal cord to its target (Fig. 22.9).

Cervicomedullary tumors, such as brainstem gliomas, present with a heterogeneous constellation of symptoms including dysphagia, dysarthria, abnormal breathing (i.e., cranial nerve deficits), and hemiparesis, spasticity, and hyperreflexia (i.e., corticospinal tract).

22.3.2.3 Pons

The pontine-medullary junction is the fold marking the transition point where the medulla becomes the pons. From this fold emerges the *abducens* (CN VI), *facial* (CN VII), and *vestibular* (CN VIII) nerves (Fig. 22.10). The pons can be divided into the *basis pontis* and the *pontine tegmentum*.

The *basis pontis* contains various nuclei and neuronal pathways. The *pontine nuclei* receive input from the cortex before projecting to the cerebellum via the pontocerebellar fibers (middle cerebellar peduncle) and play an important role in motor function. The *raphe nuclei* are serotonergic neurons which project to the cerebral cortex, hippocampus, basal ganglia, thalamus, cerebellum, and spinal cord and participate in the regulation of arousal, sleep patterns, and pain. The fibrous bundles of the corticospinal tracts also pass through the basis pontis. *Locked in syndrome*, which is characterized by paralysis (excluding ocular) and intact cognitive function, is the consequence of isolated infarction or injury to the basis pontis and sparing of the pontine tegmentum.

Locked in syndrome, which is characterized by paralysis (except for ocular) and intact cognitive function, is the consequence of isolated infarction or injury to the basis pontis and sparing of the pontine tegmentum.

The *pontine tegmentum* is extremely complex and contains a variety of tracts and cranial nerve nuclei. The *spinothalamic tract*, *medial lemniscus*, and *medial longitudinal fasciculus* are three of the tracts found passing through the pontine tegmentum. Nuclei for the abducens (CN VI) and facial (CN VII) nerves and their associated pathways are also located here. Intracranial hypertension can cause compression of the abducens nerve (CN VI) and inward deviation of the affected eye. Portions of nuclei and the various projections for the trigeminal (CN V) (Fig. 22.11) and auditory (CN VIII) pathways are located and pass through this region of the brainstem. The spinal tract of cranial nerve V (pain, temperature and touch from the face) synapses on the spi-

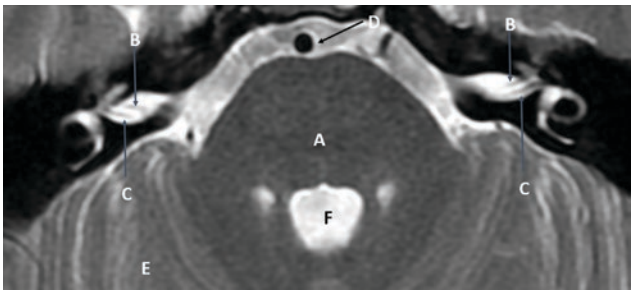


Fig. 22.10 Axial T2-weighted image of the infratentorial compartment showing pons (A). Notice cranial nerves VII (B) and VIII (C) in bilateral internal auditory canals. Basilar artery (D). Cerebellum (E). Fourth ventricle (F)

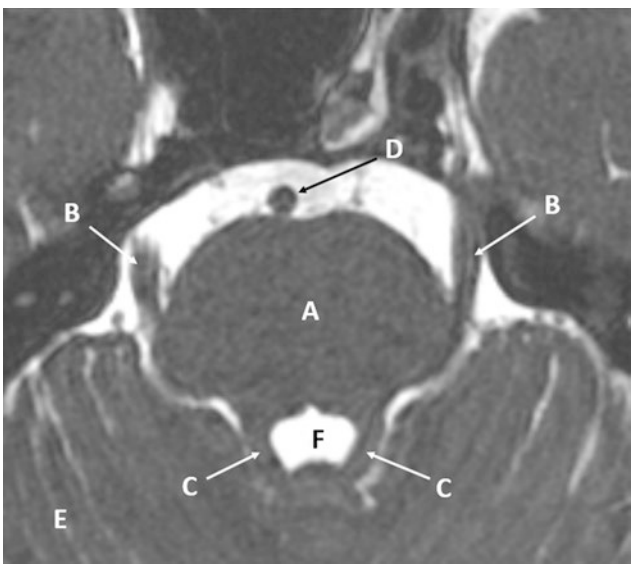


Fig. 22.11 Axial T2-weighted image of the infratentorial compartment showing pons (A). Trigeminal nerves (B). Superior cerebellar peduncles (C). Basilar artery (D). Cerebellum (E). Fourth ventricle (F)

nal nucleus of cranial nerve V before crossing and ascending to the thalamus. The medial longitudinal fasciculus contains projections from the vestibular nucleus that extend to the abducens, trochlear, and oculomotor nuclei to regulate head and gaze positioning.

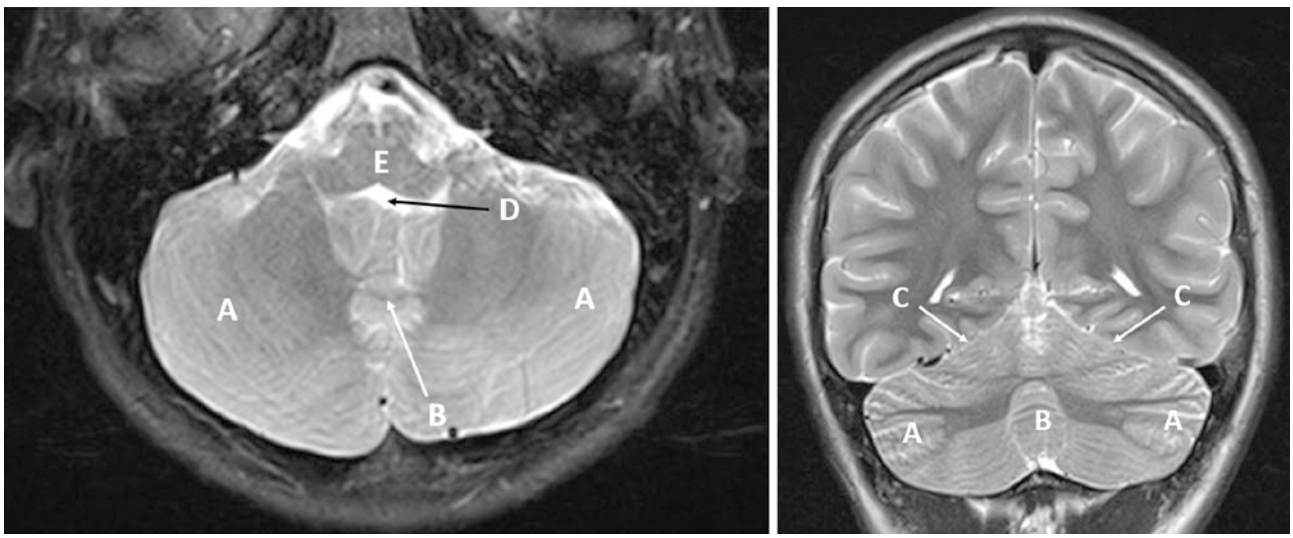
Osmotic Demyelination Syndrome, also referred to as central pontine myelinolysis, described in patients who have been treated for prolonged hypo-osmotic state (e.g., hyponatremia), is the consequence of the rapid correction of osmolarity and results in intracranial cellular shrinkage. Oligodendrocytes in the basal ganglia, thalamus, and most commonly the pons are principally affected, thus resulting in profound demyelination. Classically patients are found to have flaccid paralysis and bulbar signs secondary to injury to the corticospinal and corticobulbar tracts, respectively.

22.3.2.4 Cerebellum

The cerebellum is located in the posterior fossa, adjacent to the midbrain, pons, medulla, and fourth ventricle, which lie anteriorly. The cerebellum is separated from the occipital lobe of the cerebral cortex by the tentorium cerebelli (◘ Figs. 22.7 and 22.12), which is a reflection of the dura between the two structures. Because the brainstem and cerebellum both lie below the tentorium cerebelli, they are referred to as infratentorial. The surface of the cerebellum is distinct from other structures due to the horizontally oriented folds or *folia*.

The cerebellum is divided into two hemispheres by the *vermis* (◘ Fig. 22.12). Afferent and efferent pathways to and from the brainstem and spinal cord travel through the three pairs of *cerebellar peduncles* (superior, middle, and inferior), which comprise much of the lateral walls of the fourth ventricle. The cerebellum is further divided into the cerebellar cortex and the cerebellar white matter.

The primary efferent pathways arise from the various pairs of *deep cerebellar nuclei* in the cerebellar white matter. The deep cerebellar nuclei receive excitatory and inhibitory input from within the cerebellar cortex as well as external inputs from the brainstem and spinal cord that modulate efferent activity. Efferent neurons project to the contralateral red nuclei and thalamic nuclei before continuing to the motor cortex. This complex anatomic relationship results in "double crossing," where cerebellar efferent fibers cross to reach the



◘ **Fig. 22.12** Axial (left) and coronal (right) T2-weighted images of the infratentorial compartment showing cerebellar hemispheres (A) and vermis (B). Tentorium cerebelli (C). Fourth ventricle (D). Medulla (E)

motor cortex and descending motor pathways then cross to reach their effector site. Consequently, insult or injury to the cerebellum results in ipsilateral motor deficits.

The primary functions of the cerebellum include control of muscle tone and equilibrium through its network of connections with the vestibular system and the spinal cord and regulation of voluntary movement through its projections to the motor cortex. The cerebellar hemispheres are responsible for ipsilateral movement, tone, and coordination, while the vermis is responsible for truncal tone and coordination.

The primary role of the cerebellum includes modulation of ipsilateral tone, coordination, and movement. Lesions may produce, ataxia, hypotonia, dysmetria, and tremor.

Injury or insult (e.g., ischemia, tumor, trauma, inflammation, metabolic, degenerative conditions) to the cerebellum may result in a variety of ipsilateral findings which include:

- Ataxic gait-typically falling to the side of the lesion or insult
- Hypotonia
- Dysmetria-inability to position an extremity at a specific location in space as demonstrated with finger to nose test
- Intention tremor
- Dysdiadochokinesia – impaired rapid alternating movements

22.3.2.5 Midbrain

Transtentorial herniation, which occurs in the setting of severe elevation in intracranial pressure, can result in compression of the oculomotor nerve, loss of parasympathetic input, unopposed sympathetic input, and blown pupil.

The midbrain (Fig. 22.13) is the smallest region of the brainstem and is located caudally where the brainstem transitions into the cerebrum. Various nuclei (red, locus coeruleus, facial and hypoglossal) and ascending and descending pathways including the corticobulbar pathways of cranial nerves VII and XII are found in the brainstem. Characteristic features of the midbrain and their respective role include the *superior colliculi* (vision and reflexive eye movements), *inferior colliculi* (auditory and sound localization), and the *oculomotor nerve* (CN III), which exits along the ventral surface adjacent to the temporal lobe. The oculomotor nerve is accompanied by parasympathetic nerve fibers, which counteract sympathetic input from the cervical sympathetic ganglia to regulate pupillary dilation. Transtentorial herniation, which occurs in the setting of severe elevation in intracranial pressure, can result in compression of the oculomotor nerve, loss of parasympathetic input, unopposed sympathetic input, and blown pupil. The *substantia nigra* is also found in the midbrain,

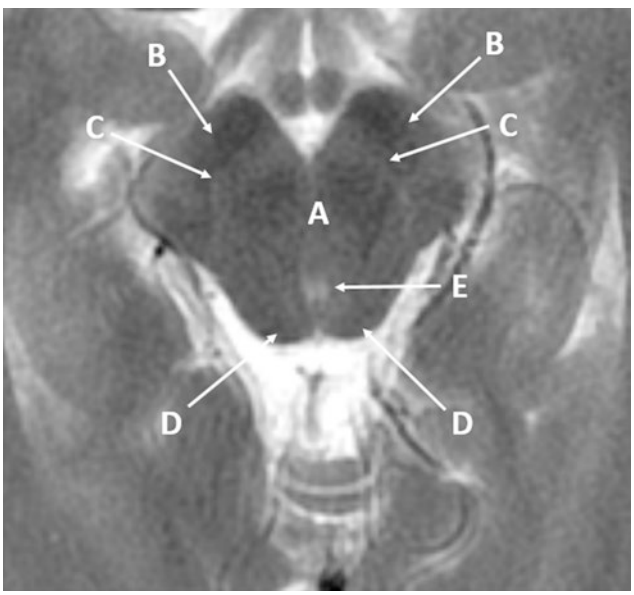


Fig. 22.13 Axial T2-weighted image of the infratentorial compartment showing midbrain (A) and its parts. Tegmentum (B). Substantia nigra (C). Tectum (D). Aqueduct of sylvius (E)

where it receives afferent input from the cortex before projecting its dopaminergic fibers to the basal ganglia (initiation of voluntary movement), the limbic system (reward and emotion), temporal lobe (memory), and frontal lobe (thought).

Bell's palsy is the consequence of injury or insult (e.g., inflammation) to the facial nerve which results in complete loss of ipsilateral motor function (upper and lower face), whereas contralateral upper face motor function is spared in the setting of stroke due to presence of ipsilateral cortical input.

The *facial nucleus* is divided into two parts, the upper and lower, which directs motor function of the upper and lower facial muscles, respectively. The upper portion receives bilateral cortical input, whereas the lower portion receives only contralateral cortical input. The importance of this distinguishing feature can be demonstrated when differentiating a Bell's palsy from a stroke. Bell's palsy is the consequence of injury or insult (e.g., inflammation) to the facial nerve which results in complete loss of ipsilateral motor function (upper and lower face), whereas contralateral upper face motor function is spared in the setting of stroke due to presence of ipsilateral cortical input.

22.3.2.6 Reticular Formation

The reticular formation is discussed separately, because it is not a distinct structure of the brainstem, but rather a network of neurons and associated projections that run through the brainstem and play a key role in arousal and level of consciousness. Because of this role, it is often referred to as the *reticular activating system*. The reticular formation functions through a series of ascending and descending pathways. Ascending pathways, consisting of serotonergic and noradrenergic neurons, project to the hypothalamus and the intralaminar and reticular nuclei of the thalamus before continuing to various locations throughout the cortex to regulate wakefulness and awareness. Neuronal pathways from the reticular formation to neurons in the hypothalamus play a central role in regulating the initiation of sleep and sleep cycles. Injury to the reticular formation, even in the absence of cortical injury, will often result in coma. Additional causes of coma to be considered within the differential diagnosis include global cerebral injury (e.g., ischemia, hypoxia), metabolic abnormalities (e.g., acidosis, hypoglycemia, hepatic failure, uremia), CNS inflammation or infection, and toxic ingestions.

Descending pathways of the reticular formation participate in the coordination of movement, sensation, and body position and regulate cardiopulmonary responses to changes in oxygenation and blood pressure.

The descending pathways of the reticular formation also serve a variety of functions, including:

- Coordination of movement, such as swallowing
- Coordination of complex reflexes important for maintaining body positioning relative to gravity and ambulation
- Coordination of movement and sensation
- Regulation of visceral and autonomic functions, such as respiratory and cardiovascular responses to changes in oxygen and blood pressure, respectively

The reticular formation is a network of ascending and descending pathways traveling through the brainstem with the former modulating level of consciousness and arousal.

Paroxysmal sympathetic hypersensitivity describes hyperactive sympathetic and motor activity occurring as a result of injury to inhibitory pathways originating in the midbrain.

Paroxysmal Sympathetic Hypersensitivity (PSH) is the more recent term for dysautonomia or autonomic storming in the setting of secondary brain injury. Although this can occur due to a variety of different brain injuries (e.g., encephalitis, traumatic brain injury, ischemia, diffuse axonal injury), its more severe forms occur with injury to the periaqueductal gray matter found within the tegmentum of the midbrain. Typically, this is a diagnosis of exclusion because patients demonstrate non-specific symptoms including both sympathetic hyperactivity (e.g., tachycardia, hypertension, tachypnea, hyperthermia, sweating) and motor hyperactivity (e.g., dystonia, posturing) in response to noxious and non-noxious stimuli. Although various theories exist, there has been a consensus that PSH is the result of the severing of inhibitory pathways originating from the midbrain, thus creating an imbalance between inhibitory and excitatory forces modulating sympathetic tone.

22.3.2.7 Cerebrum

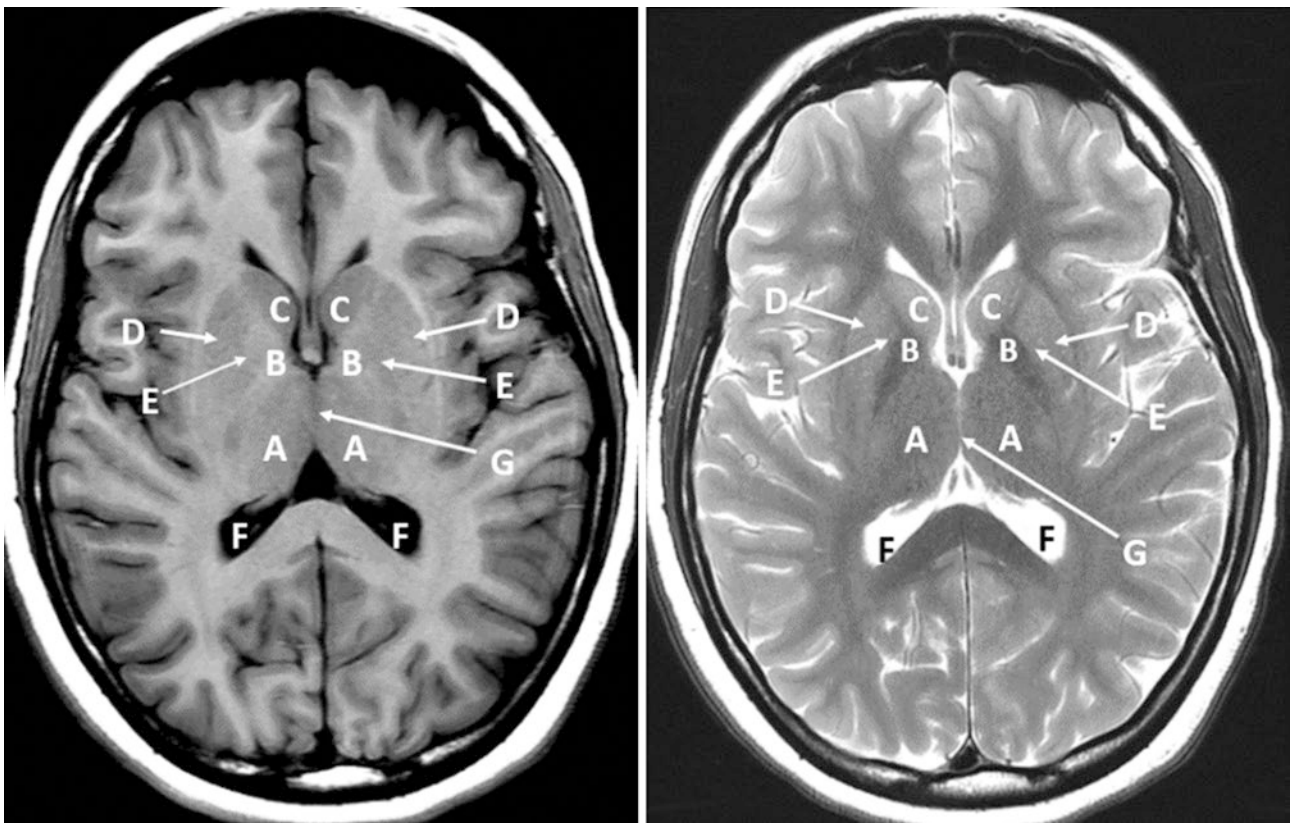
The cerebrum is the largest and most rostral division of the CNS. It develops from the embryonic prosencephalon and is further subdivided into the *diencephalon* (thalamus, hypothalamus, subthalamus and epithalamus), *basal ganglia*, and *cerebral hemispheres*.

Diencephalon

The *thalamus* (◘ Figs. 22.14 and 22.15) is a mass of nuclei that lies above the medial and lateral geniculate bodies, which receive auditory and visual input. The thalamus serves as the primary relay station for sensory pathways and coordinates motor activity through its network of connections with the basal ganglia and cerebellum.

Functionally, the thalamus is divided into the following five groups of nuclei:

- The *thalamic motor nuclei*, which relays motor information from the cerebellum and basal ganglia to the motor cortex.
- The *sensory nuclei*, which includes the ventral posterolateral (VPL), ventral posteromedial (VPM), and the lateral and medial geniculate bodies and receives sensory input from the body, face, eyes, and inner ear.
- The *anterior limbic nuclei* receive input from the mamillary bodies and cingulate gyrus and play a role in memory and arousal.
- The *dorsomedial nucleus* receives input from the olfactory cortex and amygdala and has projections to the prefrontal cortex and hypothalamus. It also plays a role in memory development.



◘ **Fig. 22.14** Axial T1 (left)- and T2 (right)-weighted images of the brain showing thalami (A). Internal capsules (B). Caudate nuclei (C). Putamina (D). Globus pallidus (E). Lateral ventricles (F). Third ventricle (G)

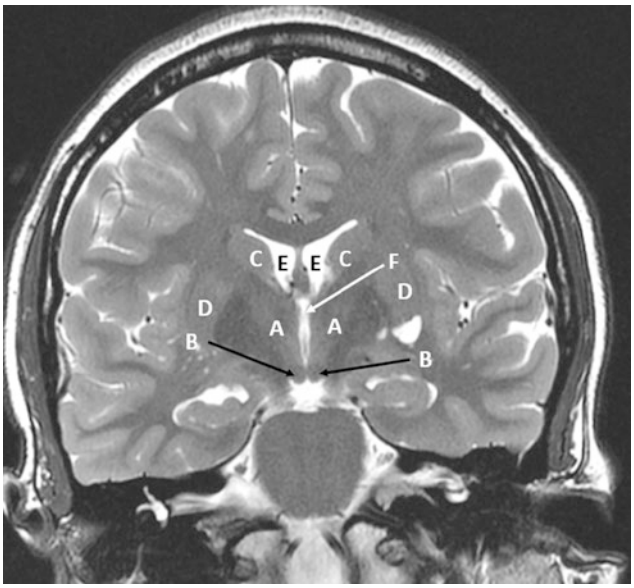


Fig. 22.15 Coronal T2-weighted image of the brain showing thalami (A). Mammillary bodies of hypothalami (B). Caudate nuclei (C). Putamina (D). Lateral ventricles (E). Third ventricle (F)

- The *multimodal nuclei* (pulvinar, posterolateral, and dorsolateral) have a widespread network of connections including the frontal, parietal, and temporal lobes and serve a variety of roles including regulating memory, emotion, and integration of sensory information.

Injury to the thalamus can occur in a variety of settings including hypoxic-ischemic injury, infectious encephalitis (e.g., influenza, mycoplasma), inflammatory (e.g., SLE), and stroke (e.g., basal artery occlusion). Consequences of thalamic insults can be widespread due to its numerous roles, but may include sensory loss, decreased level of consciousness, coma, emotional disturbances, and motor dysfunction.

The *hypothalamus* (Figs. 22.7 and 22.15) is located inferior to the thalamus, and although it is a small structure, it serves a wide variety of complex functions including modulation of autonomic function, serum osmolality, circadian rhythm, hunger, temperature, and emotion. The hypothalamus is connected to both the *anterior pituitary* or adenohypophysis and the *posterior pituitary* or neurohypophysis (Fig. 22.7) through vascular and axonal connections respectively. The *supraoptic and paraventricular nuclei* synthesize precursors to oxytocin and antidiuretic hormone, which are transported to the posterior pituitary, where they are released into the circulation. Other nuclei of the hypothalamus produce several inhibitory and releasing factors, which are transported via the vascular hypophyseal portal system to the adenohypophysis where they influence the release of a variety of anterior pituitary hormones:

- Adrenocorticotropic hormone (ACTH)
- Thyroid Stimulating hormone (TSH)
- Growth hormone (GH)
- Luteinizing and follicle-stimulating hormones
- Prolactin

The presence of panhypopituitarism (i.e., diabetes insipidus, hypothyroidism, adrenal insufficiency, and hyperprolactinemia), aggressive behavior, emotional instability, and anorexia or polyphagia should raise the concern for a hypothalamic mass. Resection of these masses may result in persistent panhypopituitarism due to injury to the pituitary gland during surgery.

Cerebral Hemispheres

The largest and most rostral region of the central nervous system is the cerebral hemispheres, which is composed of the *cerebral cortex*, *basal ganglia*, *and hippocampus*. The cerebral hemispheres are recognized by the complex system of folds (gyri) and spaces separating these folds (sulci), which allows the increased surface area of the cortex (approximately 2.5 square feet) to fit within the confined cranial vault (approximately 0.5 square feet).

Each cerebral hemisphere is divided into four lobes:

- *Frontal lobe*: The most rostral portion of the cerebrum. The frontal lobe is separated from the parietal lobe by the central sulcus (Figs. 22.16, 22.17, and 22.18).
- *Parietal lobe*: It extends from the central sulcus to the parieto-occipital sulcus posteriorly and the deep lateral fissure inferolaterally (Figs. 22.18 and 22.19).
- *Occipital lobe*: It lies posterior to the parieto-occipital sulcus (Figs. 22.18, 22.19, and 22.21).
- *Temporal lobe*: It continues inferolaterally from the deep lateral fissure (Figs. 22.20, 22.21, and 22.22).

Although anatomically the cerebral hemispheres are essentially symmetrical, some functions of the cerebral hemisphere are specific to one hemisphere. The frontal lobe can be divided into the following four cortices:

- *Primary motor cortex*: It is located along the precentral gyrus, which is anterior to the central sulcus and controls voluntary movement on the contralateral side of the body. Upper motor neurons descend, cross at the level

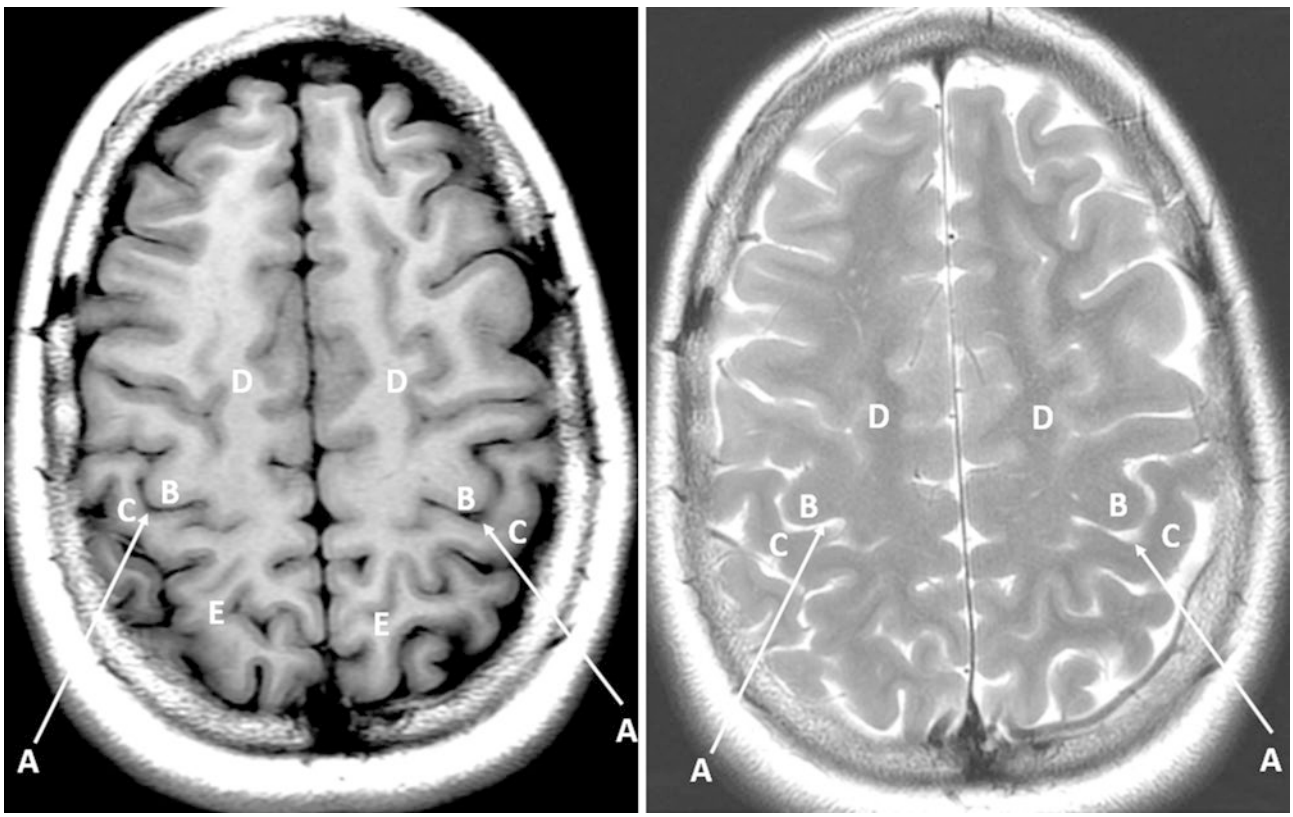


Fig. 22.16 Axial T1 (left)- and T2 (right)-weighted images of the brain showing central sulci (A). Precentral gyri (B). Postcentral gyri (C). Frontal lobes (D). Parietal lobes (E)

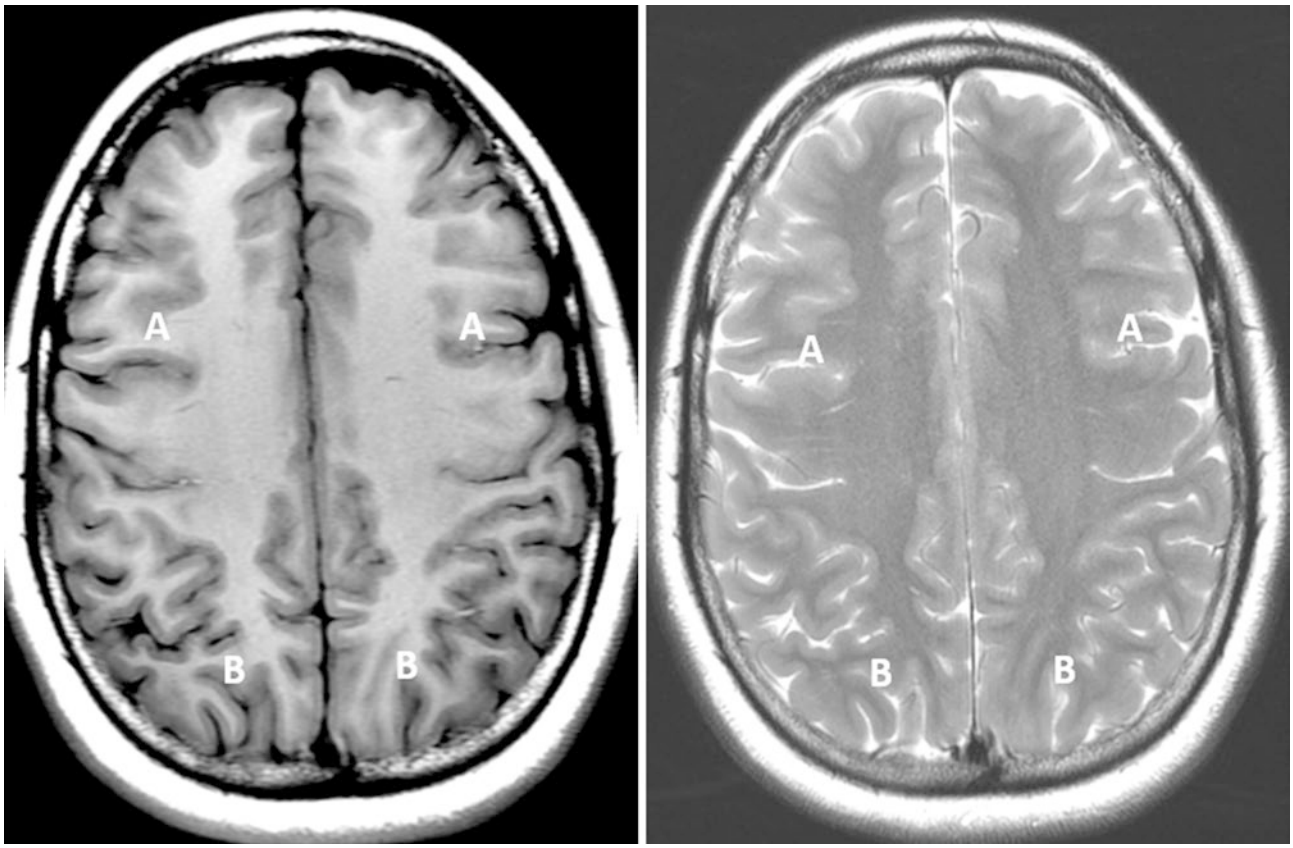


Fig. 22.17 Axial T1 (left)- and T2 (right)-weighted images of the brain showing frontal lobes (A) and parietal lobes (B)

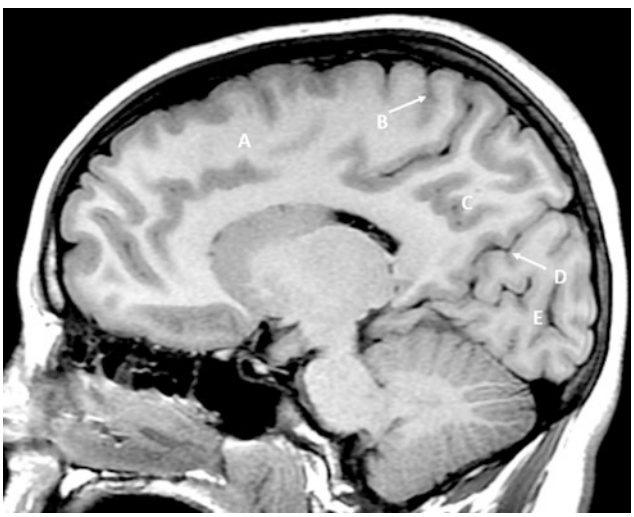


Fig. 22.18 Sagittal T1-weighted image of the brain showing frontal lobe (A). Central sulcus (B). Parietal lobe (C). Parieto-occipital sulcus (D). Occipital lobe (E)

of the medulla, and continue as the lateral corticospinal tract where they synapse on lower motor neurons.

- *Prefrontal cortex*: It comprises the remainder of the frontal lobe anterior to the primary motor cortex and is responsible for personality, planning, and insight.
- *Broca's area*: It is located in the frontal lobe of one of the hemispheres (typically left) and is responsible for regulating spoken and written language.
- *Premotor cortex*: It is located just anterior to the precentral gyrus and posterior to the prefrontal cortex and is responsible for planning, coordination, and initiation of movement.

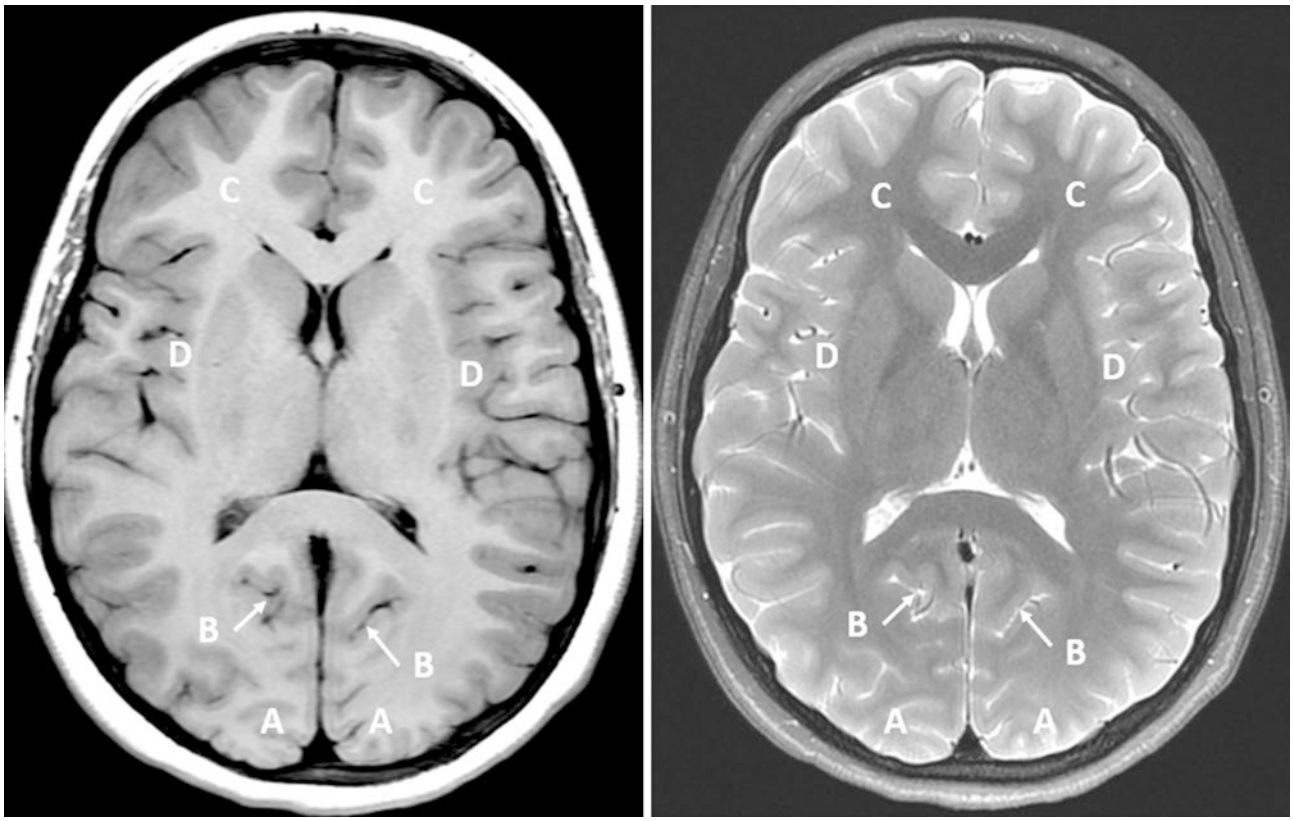


Fig. 22.19 Axial T1 (left)- and T2 (right)-weighted images of the brain showing occipital lobes (A). Parieto-occipital sulci (B). Frontal lobes (C). Insula (D)

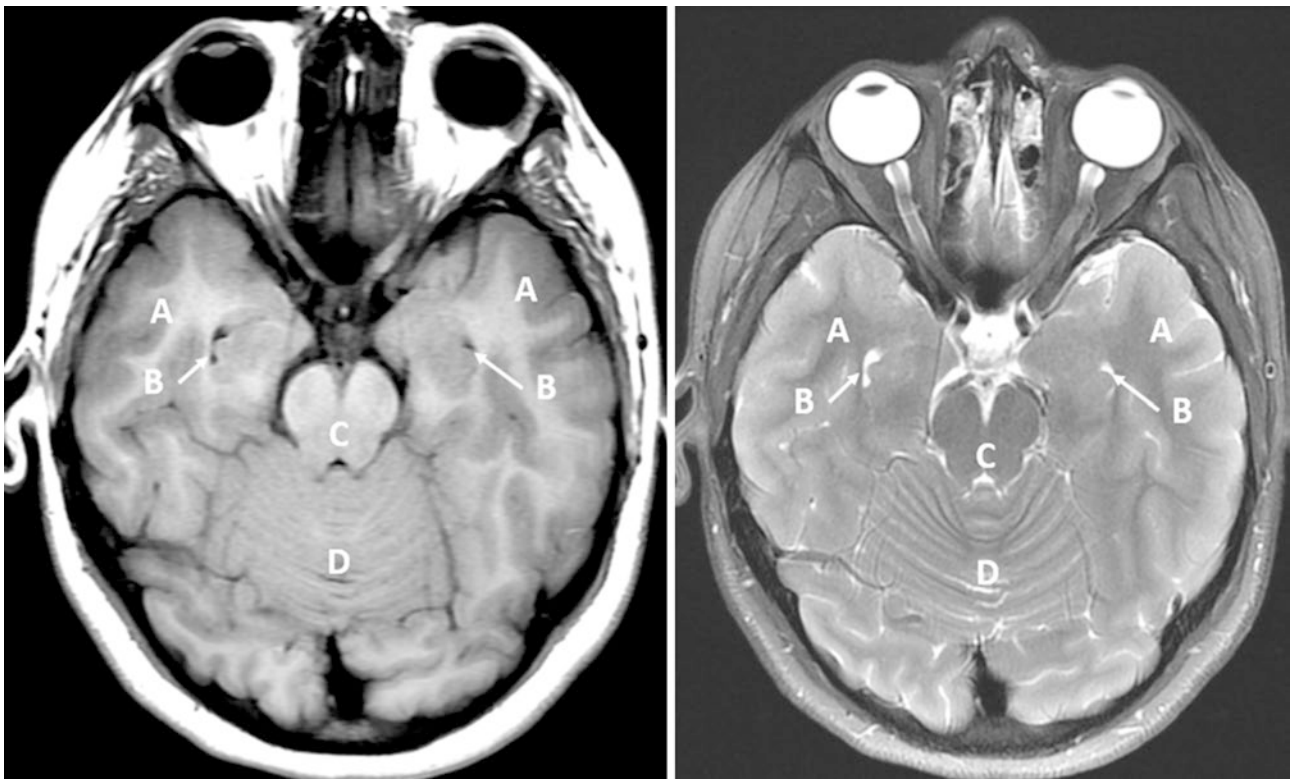


Fig. 22.20 Axial T1 (left)- and T2 (right)-weighted images of the brain showing temporal lobes (A). Temporal horns of the lateral ventricles (B). Midbrain (C). Cerebellum (D)

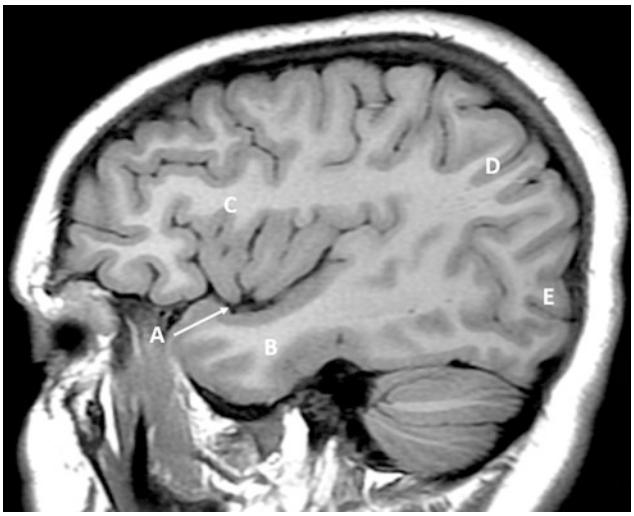


Fig. 22.21 Sagittal T1-weighted image of the brain showing deep lateral (a.k.a. Sylvian) fissure (A). Temporal lobe (B). Frontal lobe (C). Parietal lobe (D). Occipital lobe (E)

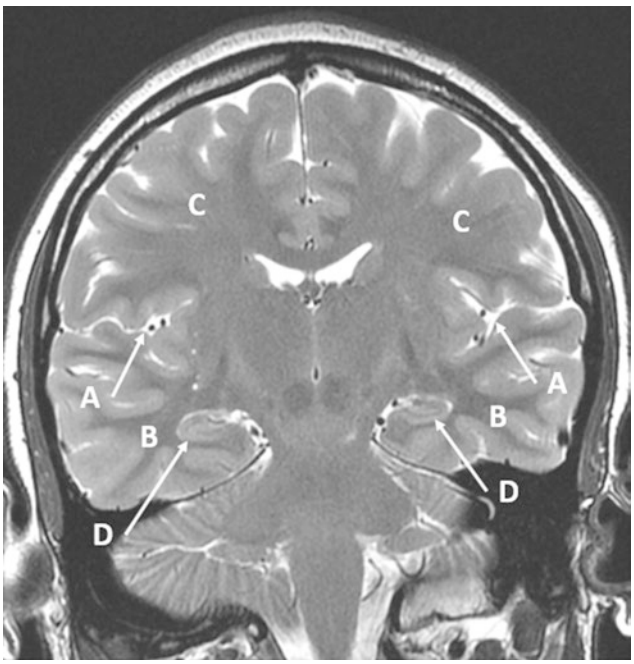


Fig. 22.22 Coronal T2-weighted image of the brain showing deep lateral (a.k.a. Sylvian) fissure (A). Temporal lobes (B). Frontal lobes (C). Hippocampi (D)

The parietal lobe contains the primary somatosensory cortex within the *post-central gyrus*, which lies posterior to the central sulcus (Figs. 22.16, 22.17, and 22.18). This area is responsible for tactile and proprioceptive sensory information from the contralateral side of the body. Posterior to the primary somatosensory cortex are asymmetric areas with very specific lateralizing functions. The left side is responsible for language processing and comprehension, while the right side is responsible for perception of space and spatial orientation.

The occipital lobe is committed to regulating vision and contains the primary visual cortex and various secondary visual areas.

The temporal lobe serves a variety of functions and includes the primary auditory cortex, the hippocampus (Fig. 22.22), and limbic systems, which regulate learning, memory, and emotion.

Basal Ganglia

The term "basal ganglia" is somewhat of a misnomer as it consists of various nuclei rather than a collection of ganglia. The basal ganglia lie in the deep gray matter of the cerebral hemisphere and surround the thalamus. It consists of the *caudate nucleus*, *putamen*, *and globus pallidus* (◘ Figs. 22.14 and 22.15). The putamen and the globus pallidus are collectively referred to as the *lenticular nuclei*, while all three are sometimes referred to as the *corpus striatum* because of their striped appearance.

The positional relationship of the basal ganglia and various other structures to each other on imaging may vary depending on the axial plane by which they are being viewed.

The caudate is continuous with the putamen and travels along the inferior-lateral aspect of the lateral ventricle before curving posteriorly, traveling anteriorly into the temporal lobe and ending at the amygdala. The lenticular nuclei (putamen and globus pallidus) are separated from much of the caudate nucleus by the internal capsule and lie just medial to the insula and external capsule.

As noted previously, the basal ganglia have a striped appearance due to a rich network of myelinated fibers that travel to the basal ganglia from the cortex, thalamus, substantia nigra, and subthalamic nuclei. This interconnected network is often referred to as the *extrapyramidal system* and serves as the foundation for the basal ganglia's regulation of motor functioning. The putamen receives somatosensory and motor input from the cortex before projecting to the thalamus and globus pallidus, which then completes the loop by projecting back to the cortex. The globus pallidus is the primary outflow nucleus of the basal ganglia, but also functions as the inhibitory regulator of the loop that exists between the cortex, basal ganglia, thalamus, and cortex. Patients with poor motor control such as tremor or rigidity (e.g., Parkinson's disease) may have deep brain stimulation performed on the globus pallidus to inhibit some of these hyperactive movements.

Although regulation of motor activity is one of the primary roles served by the basal ganglia, connections with the prefrontal cortex and the caudate nucleus also allow the basal ganglia to play a role in cognitive functioning. Areas containing these connections are at risk for degeneration following hypoxic-ischemic insults.

The basal ganglia are very susceptible to injury such as from hypoxia, hypoglycemia, carbon monoxide poisoning, and inborn errors of metabolism. Clinical signs of injury are non-specific and include mental status changes, lethargy, or irritability. Movement disorders may be seen early on with acute injuries but are more commonly seen with degenerative processes within the basal ganglia (e.g., Juvenile Huntington disease).

The basal ganglia are very susceptible to injury such as from hypoxia, hypoglycemia, carbon monoxide poisoning, and inborn errors of metabolism.

22.3.2.8 Vascular Supply to the Brain and Spinal Cord

Arterial Blood Supply to the Brain

Arterial blood flow to the brain can be divided into an anterior (from the internal carotid) and posterior (from the vertebral arteries) circulation. The *internal carotid artery* arises bilaterally from the common carotid artery and gives rise to various branches as outlined in ◘ Figs. 22.23, 22.24, and 22.25.

The internal carotid artery courses through the carotid canal, the temporal bone, and the cavernous sinus before branching off into various directions. Occlusion of the *anterior cerebral artery* results in injury to the medial portions of the primary sensory and motor cortices (i.e., legs, trunk and shoulders). Because of the broad distribution of the *middle cerebral artery*, injury can be neurologically devastating. *Watershed areas* are regions perfused by the most distal branches of the respective arteries and are therefore highly susceptible to global ischemic insults (e.g., cardiac arrest, hypotension). The region where the branches of the anterior cerebral artery and middle cerebral artery converge is one such area susceptible to global ischemia.

Watershed areas are regions perfused by the most distal branches of the respective arteries and are therefore highly susceptible to global ischemic insults.

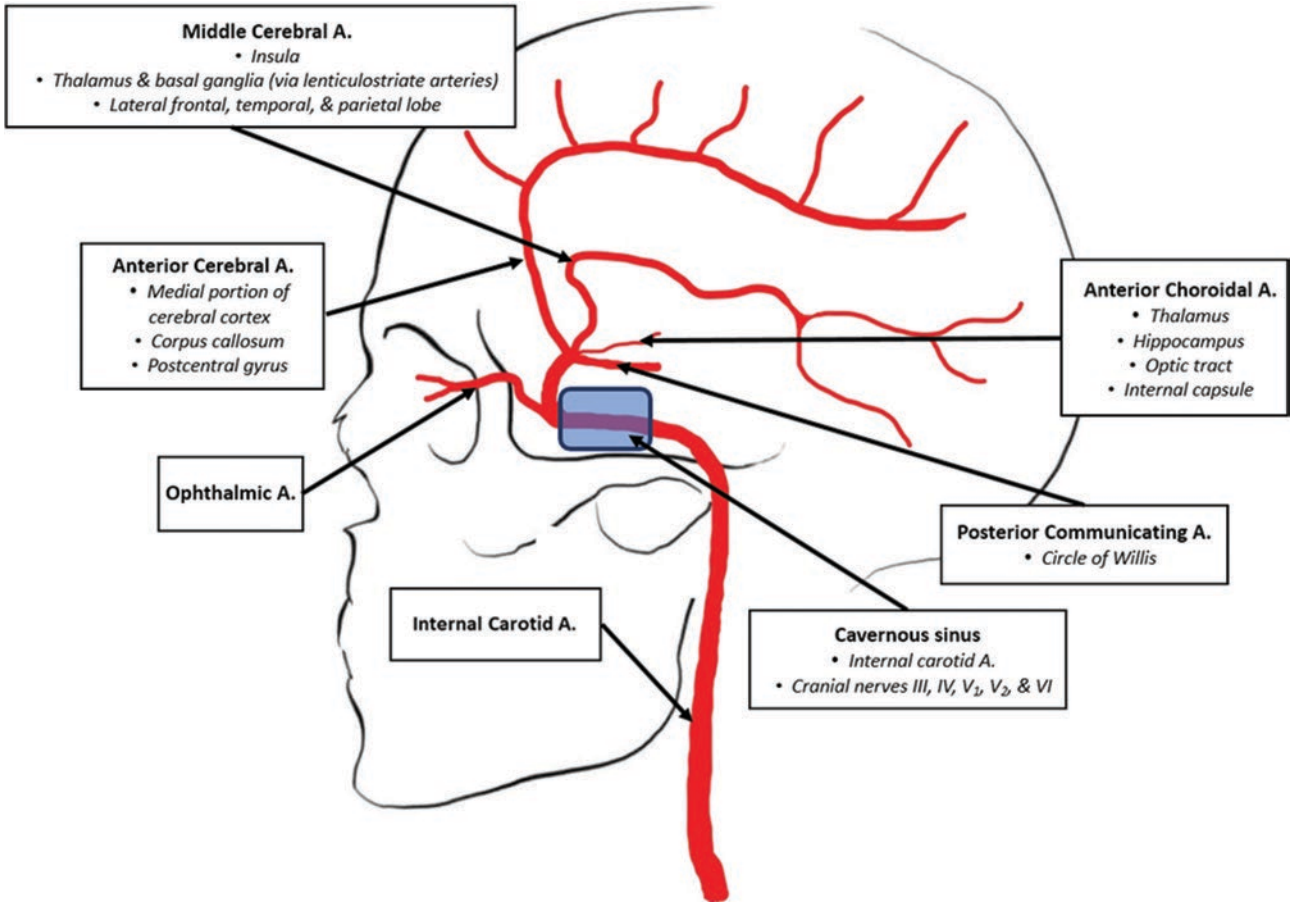


Fig. 22.23 Anterior circulation to the brain and the branches of the internal carotid artery

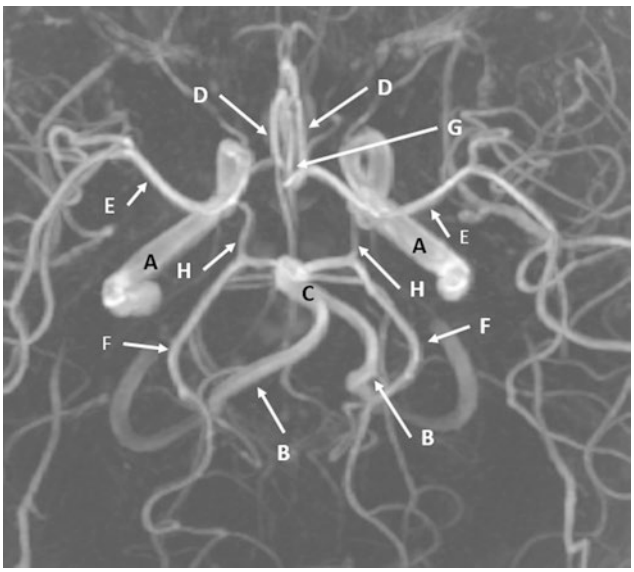


Fig. 22.24 MR angiography image of the circle of Willis showing internal carotid arteries (A). Vertebral arteries (B). Basilar artery (C). Anterior cerebral arteries (D). Middle cerebral arteries (E). Posterior cerebral arteries (F). Anterior communicating artery (G). Posterior communicating arteries (H)

22

The paired *vertebral arteries* merge at the junction of the medulla and pons to give rise to the *basilar artery*, which runs rostrally until it branches at the level of the midbrain to give rise to the *anterior inferior cerebellar artery*, *superior cerebellar artery*, *and posterior cerebral artery* (Figs. 22.26 and 22.27). Occlusion of the posterior cerebral artery, because of its distribution, results in contralateral sensory and/or vision loss.

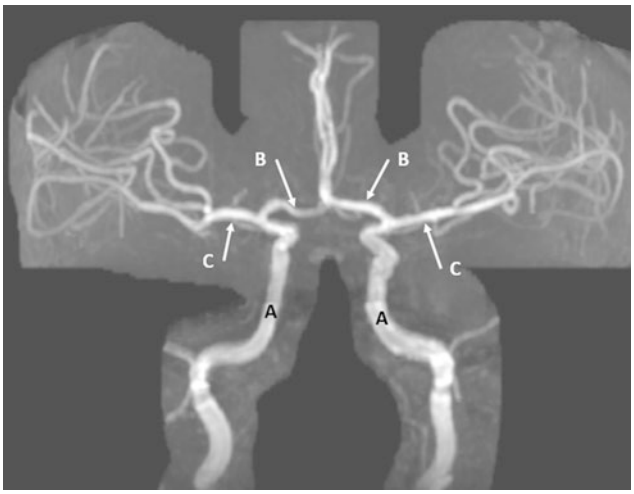


Fig. 22.25 Cerebral MR angiography image shows internal carotid arteries (A). Anterior cerebral arteries (B). Middle cerebral arteries (C)

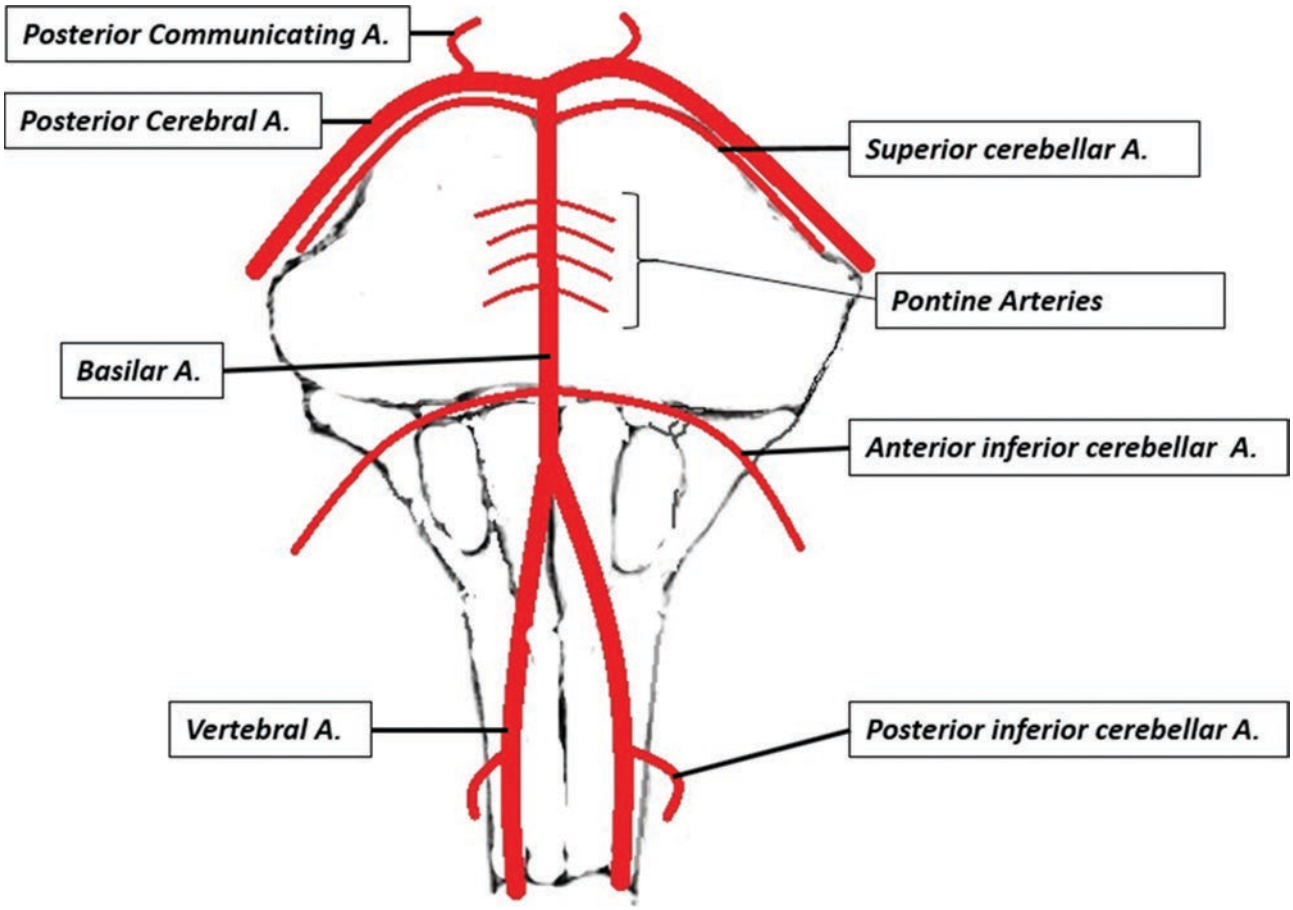


Fig. 22.26 Posterior circulation to the brain and the branches of the vertebral and basilar arteries

Arterial Blood Supply to the Spine

Arterial blood supply to the spinal cord consists of the interconnected longitudinal and segmental arterial systems, which arise from the vertebral arteries and aorta. The longitudinal system begins as the paired vertebral arteries meet to become the *anterior spinal artery*, which runs along the anterior median fissure of the spinal cord and provides the arterial blood source for the ventral two-thirds of the spinal cord. Injury or occlusion of the anterior spinal artery

Anterior spinal syndrome results in symmetric weakness and loss of pain and temperature sensation as a consequence of ischemic injury to the anterior spinal cord.

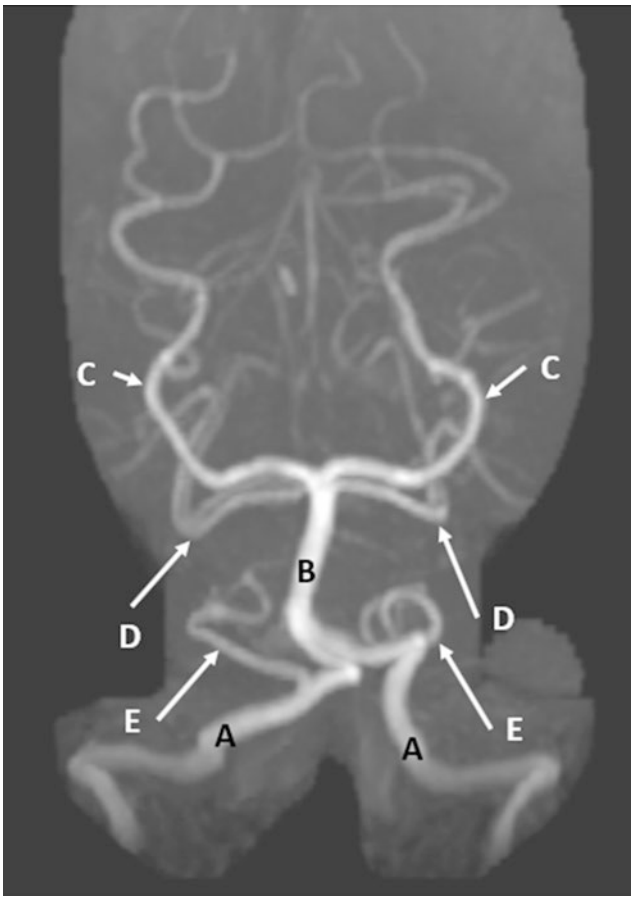


Fig. 22.27 Cerebral MR angiography image shows vertebral arteries (A). Basilar artery (B). Posterior cerebral arteries (C). Superior cerebellar arteries (D). Posterior inferior cerebellar arteries (E)

results in *Anterior Spinal Syndrome* or *Beck Syndrome*, which consists of (1) symmetric weakness, (2) loss of pain and temperature sensation, and (3) relative sparing of position and vibration sensation.

The paired *posterior spinal arteries* arise from either the posterior inferior cerebellar artery (75%) or vertebral artery (25%). These paired arteries run along the posterior column and provide the arterial blood supply for the dorsal one-third of the spinal cord. Isolated lesions are relatively uncommon because of the interconnected nature of the posterior spinal arteries and multiple contributions from the segmental arteries.

Central cord injury is a consequence of ischemic injury to the watershed areas of the interior portion of the spinal cord and results in weakness (upper extremity > lower extremity), urinary retention, and variable sensory loss.

The segmental arteries of the spinal cord arise from the vertebral and deep cervical arteries, intercostal arteries, and lumbar arteries of the cervical, thoracic, and lumbar regions, respectively (Fig. 22.28). Segmental arteries of the spinal cord are less interconnected than the longitudinal arteries and are therefore more susceptible to ischemic injury. Watershed areas include the upper thoracic region (T1-T4), lumbar region (L1), and the interior portion of the spinal cord. The interior portion of the spinal cord is a vulnerable region to hypoxic-ischemic injury, which can occur with severe cervical hyperextension, hypoxia, and vascular injury. *Central cord injury*, which is characterized by upper extremity weakness greater than lower extremity weakness, urinary retention, and variable sensory loss, is the consequence of injury to the interior portion of the spinal cord as the name implies. The *great radicular artery* or the *Artery of Adamkiewicz* provides arterial blood supply to the lower two-thirds of the thoracic spinal cord. It becomes the sole source of arterial blood flow during lumbar procedures requiring cross-clamping of the aorta.

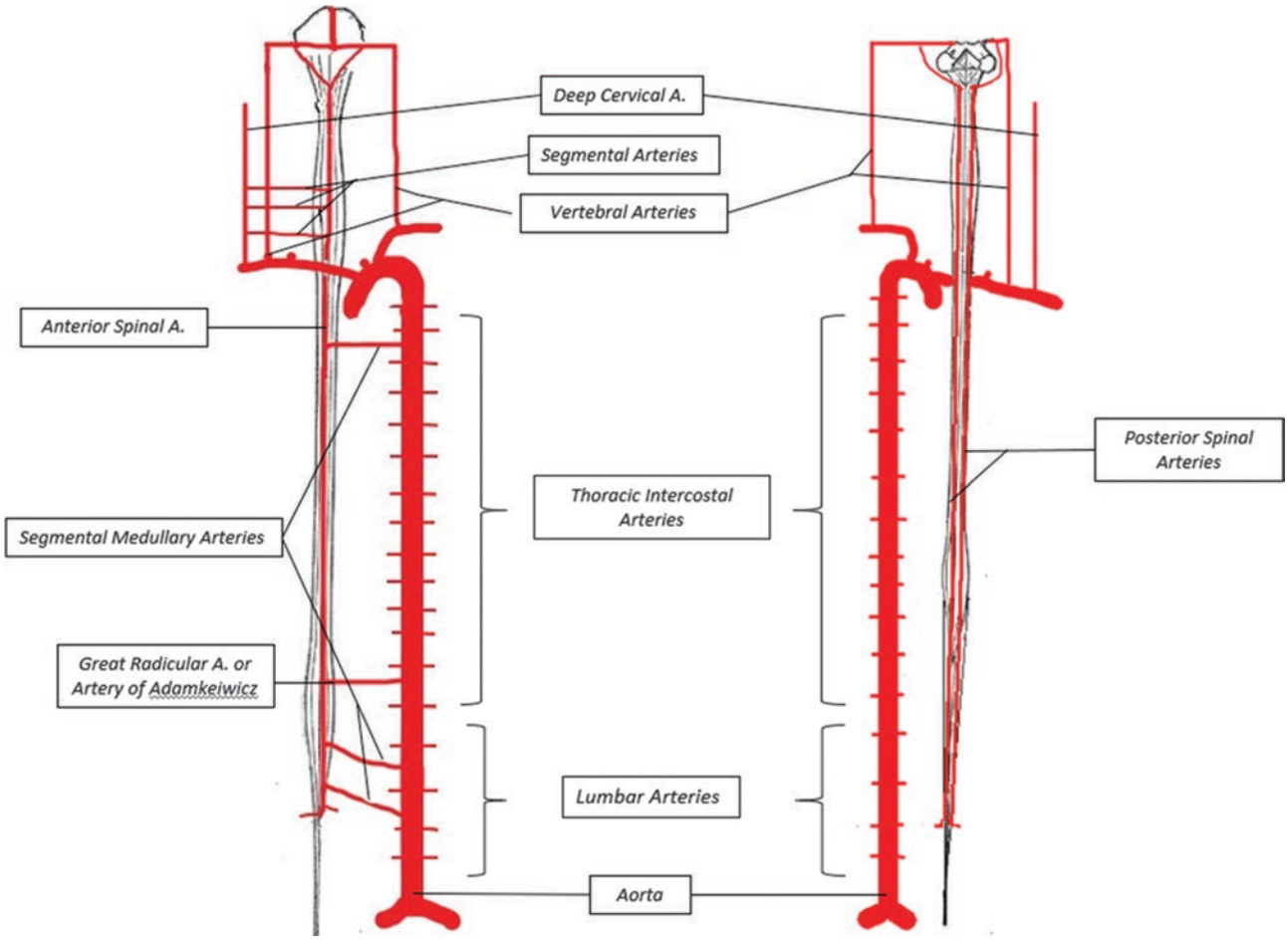


Fig. 22.28 Arterial blood supply to the spine

Cerebral Autoregulation

Cerebral blood flow (CBF) is tightly regulated to ensure the metabolic demands of the CNS are met. The CBF of a preterm infant is approximately 13–14 mL / 100 g of brain / min. This value increases with gestational age, especially in the first few days of life. Cerebral blood flow continues to increase until adolescence when it begins to slowly decline to adult levels by the second decade of life. In young adults, CBF is typically in the range of 50–60 mL/ 100 g / min. This results in a total CBF of approximately 750 mL / min or about 15% of the total cardiac output. In children, CBF is much higher (100 mL / 100 g / min). Autoregulation is the term used to describe the cerebral vasculature's ability to vasodilate or vasoconstrict in response to physiologic changes to maintain CBF. There are four primary mechanisms by which this occurs:

- Pressure autoregulation
- Oxygen-related autoregulation
- pH-based autoregulation
- Metabolic coupling

Cerebral blood flow accounts for approximately 15% of the total cardiac output.

Pressure Autoregulation

Perfusion pressure autoregulation is one of the primary mechanisms by which vascular tone is regulated to maintain cerebral blood flow. CBF is kept constant over a range of cerebral perfusion pressure (CPP = mean arterial pressure (MAP) – ICP) through myogenic mechanisms. The range of CPP

within which CBF is maintained varies with age. Adults maintain a constant CBF when the cerebral perfusion pressure is in the range of 40–160 mmHg. Cerebral blood flow increases or decreases passively when CPP is outside of these upper and lower limits. This range of CPP is narrower in neonates and infants (40–90 mmHg). Because of this narrow range, neonates and infants are at high risk of intracranial hemorrhage when CPP exceeds the upper limit and at risk of hypoxic-ischemic insult below the lower range, especially given that neonates typically have a lower MAP than older children and adults (i.e., the MAP may not fall dramatically before the CPP drops below the lower limit).

Oxygen-Related Autoregulation

It is important to avoid hypoxia (PaO_2 < 60 mmHg) in the setting of insults producing intracerebral hypertension, as hypoxic-related vasodilation could exacerbate elevations in ICP.

Local mediators in the cerebral vasculature maintain oxygen delivery by regulating CBF at various PaO_2 levels. At PaO_2 levels below 60 mmHg, there is a steep rise in CBF. It would be more accurate to describe the hypoxia-related vasodilation as a response to oxygen content rather than a specific PaO_2, which is evident when PaO_2 exceeds 60 mmHg. Above these levels, CBF varies less dramatically, because oxyhemoglobin saturation varies less with PaO_2 at the upper levels of the oxyhemoglobin dissociation curve and thus the changes in PaO_2 produce less change in oxygen content of the cerebral arterial blood flow. In the setting of hyperoxia, CBF decreases 15–20%.

pH-Based Autoregulation

pH-based autoregulation provides the rationale for hyperventilation in the setting of acute ICP elevation. There is a risk of ischemia during this time because of vasoconstriction and decreased CBF.

Response to the perivascular pH is another autoregulatory mechanism, which modifies CBF in response to pH, or more rapidly to $PaCO_2$. Between a $PaCO_2$ of 20–80 mmHg, there is a linear relationship between $PaCO_2$ and CBF, whereas for every mmHg change in $PaCO_2$, cerebral blood flow changes by approximately 4%. Cerebral arteries vasodilate in response to hypercapnia and vasoconstrict in response to hypocapnia. Unlike the other autoregulatory mechanisms, pH-based autoregulation remains relatively intact in the setting of intracranial injury (e.g., TBI, cardiac arrest) and recent studies suggest that the response persists beyond 24 h.

Metabolic Coupling

Cerebral autoregulation maintains cerebral blood flow in response to changes in cerebral perfusion pressure, oxygen content, pH (PCO_2), and metabolic demands.

Autoregulation in response to metabolic demand occurs at a local level, thus modulating cerebral blood flow to small, specific, metabolically active areas. The cerebral metabolic rate of oxygen ($CMRO_2$) and glucose (CMRGlu) correlate directly with CBF except for sensory stimulation, where the increase in CBF is proportionally greater than the increase in $CMRO_2$. This suggests neuronal activity independently triggers increases in CBF, which is the basis for functional MRI.

22.3.2.9 Ventricular System and CSF

The ventricular system (◘ Figs. 22.7, 22.12, 22.13, 22.14, 22.15, and 22.29) begins as a hollow structure within the developing neural tube and gives rise to the various ventricles and cisterns within the CNS, which bathes and cushions the brain and spinal cord with cerebral spinal fluid (CSF).

Ventricles are lined with ependymal cells interconnected by tight junctions, which contribute to the CSF- brain barrier. Ventricles also contain the choroid plexus, which produces CSF. Fifty percent of CSF is produced by the choroid plexus, while the remaining half is produced by the brain parenchyma. While CSF produced by the choroid plexus is released directly into the ventricles, CSF produced by the parenchyma crosses the ependymal lining before entering the ventricles and cisterns. Adults and children produce approximately 350 μL/min (500 mL/day or 20 mL/h).

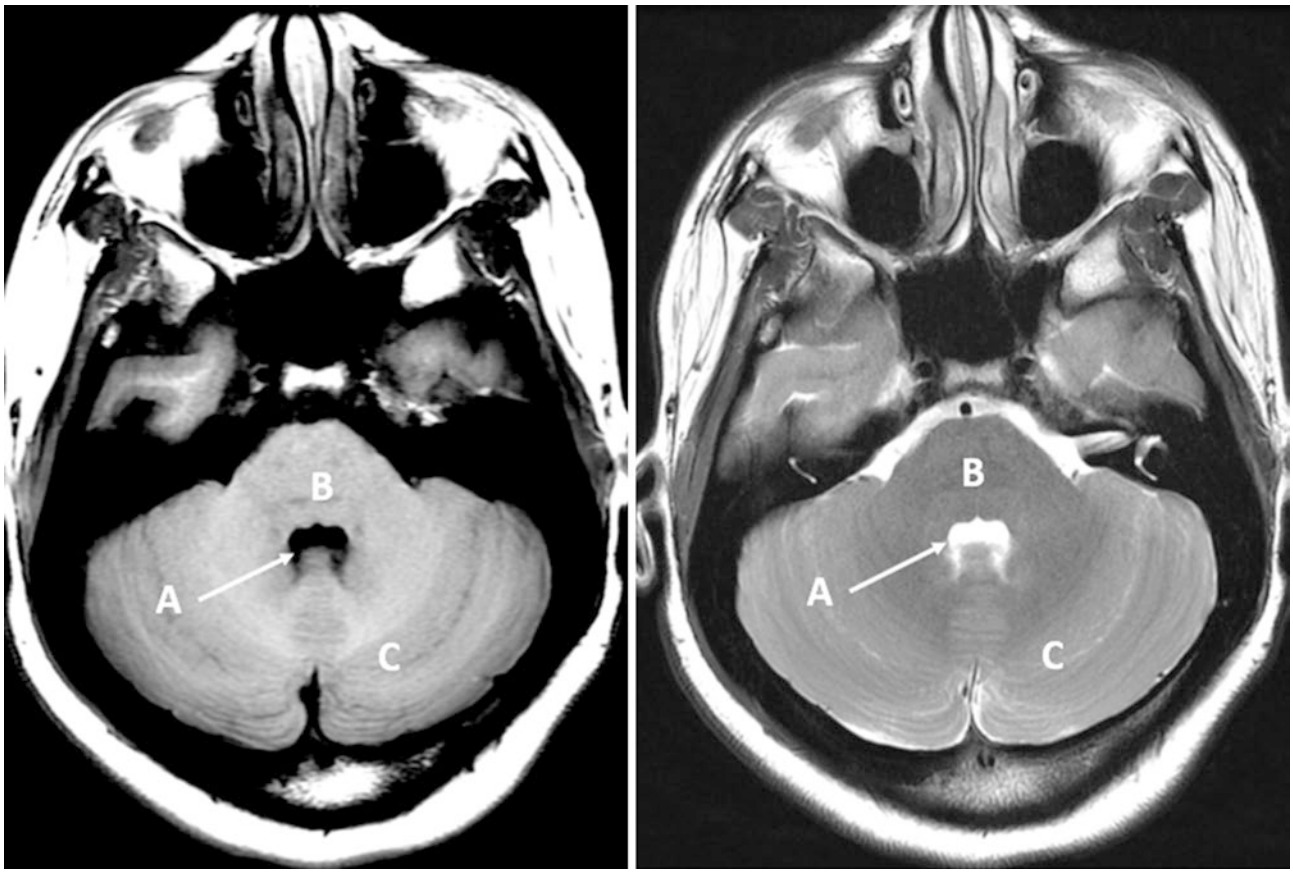


Fig. 22.29 Axial T1 (left)- and T2 (right)-weighted images of the brain showing fourth ventricle (A). Pons (B). Cerebellum (C)

Cerebral spinal fluid is produced as plasma filtered through leaky capillaries in the choroid plexus, but is tightly regulated, thus generating a fluid composition different from that of plasma with regard to the cellular, ionic and chemical makeup. For example, CSF contains very few cells, a constant protein level, and a glucose concentration that is roughly two-thirds that of plasma. Composition can be altered under a variety of conditions including infection (i.e., bacterial vs viral meningitis) or other injuries. Cerebral spinal fluid provides a buoyant milieu supporting the brain, which is the consistency of gelatin and would otherwise flatten with the force of gravity were it not for CSF within the cranial vault. Cerebral spinal fluid also provides nutrients and serves as a reservoir for metabolic waste products and toxins, thus protecting the CNS from injury.

Hydrocephalus is the consequence of CSF accumulation in response to obstruction or impaired reabsorption.

Cerebral spinal fluid flows through the ventricular system before it enters the subarachnoid space, where it is absorbed by arachnoid villi and returns to the circulation via the superior sagittal venous sinus (Fig. 22.30). Because the arachnoid villi are not fully developed during early infancy, CSF is drained through the ventricular ependyma, into the interstitial and perivascular space and then into the perineural lymphatics before returning to the circulation. This later pathway is present in all ages but plays a minor role in CSF drainage beyond early infancy. Hydrocephalus, the accumulation of CSF around the brain, is the consequence of (1) outflow obstruction within the ventricular system (e.g., tumor) or (2) impaired or obstructed reabsorption due to cellular debris surrounding the arachnoid villi (e.g., meningitis, hemorrhage). As CSF accumulates, intracranial pressure (ICP) increases, which can result in spontaneous or iatrogenic herniation (i.e., consequence of lumbar puncture in a patient with CSF obstruction above the level of the Foramen magnum).

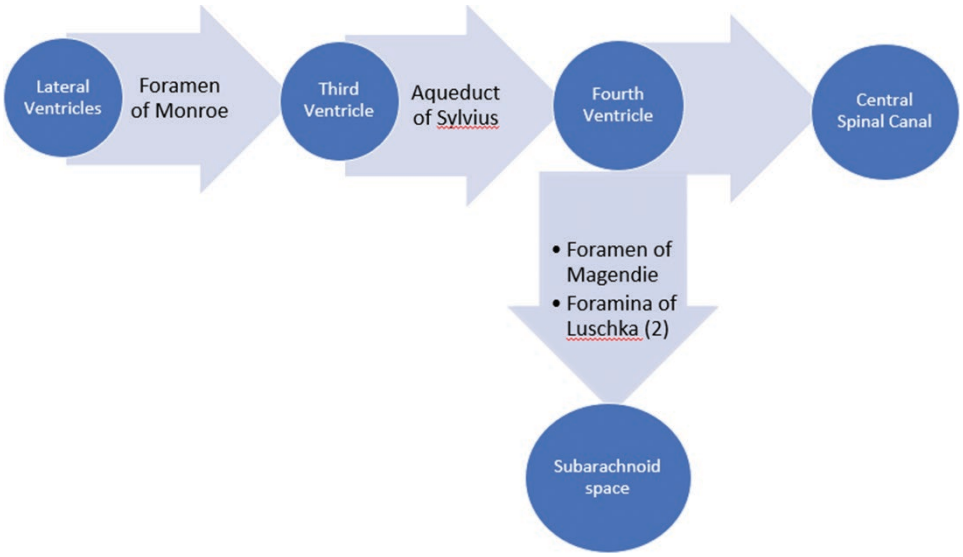


Fig. 22.30 Cerebrospinal fluid circulation

22.3.2.10 Meninges

The meninges consist of three layers of membranes which encase and protect the brain and spinal cord. These three layers include the *(1) Dura mater*, *(2) Arachnoid membrane*, *and (3) Pia mater*. Dura mater is also called *pachymeninx* and is the layer attached firmly to the skull and arachnoid layer. Between the skull and dura mater is the *epidural space*, while the *subdural space* lies between the dura mater and arachnoid layer. These spaces surrounding the dura mater are *"potential spaces"* in that no true open space exists within these layers. *Meningeal arteries* navigate through the epidural space and when injured can result in hemorrhage and an epidural hematoma. *Bridging veins* traverse the long distance across the subdural space and are more susceptible to injury, hemorrhage, and subdural hematoma formation when subjected to shear forces. The dura mater is also responsible for the formation of the cerebral venous sinuses, which are responsible for draining all the cerebral veins.

The *arachnoid membrane* is a thin layer consisting of a network of collagen fibers adhering to the overlying dura mater and is connected to the underlying pia mater via arachnoid trabeculae. The subarachnoid space is the only true fluid-filled space around the brain containing CSF. Arachnoid villi are specialized projections that protrude into the dural venous sinuses and return CSF to the venous circulation as described in the previous section. Cerebral arteries and veins run within the subarachnoid space before penetrating the cerebral surface. Injury to these vessels gives rise to subarachnoid hemorrhages and hematomas.

The *pia mater* is the thinnest and most delicate of the meningeal layers and adheres to surface of the brain and cerebral blood vessels. *Virchow-Robin spaces* are potential spaces around the blood vessels enveloped by the pia mater and can serve as a reservoir for malignant cells in the setting of pediatric leukemia or lymphoma, thus necessitating CNS irradiation and chemoprophylaxis.

22.3.3 Peripheral Nervous System

The peripheral nervous system consists of the *(1) somatic* and *(2) autonomic nervous system*. The somatic nervous system conveys information to and from the muscle and skin via efferent and afferent nerve fibers, respectively. Efferent fibers arise from neurons within the spinal gray matter before exiting the ven-

tral root of the spinal cord en route to its muscle and skin targets. Afferent nerve fibers arise from peripheral sensory receptors and enter the dorsal root ganglia. Both efferent and afferent nerve fibers travel together to and from their targets via the dorsal and ventral rami. Disorders of the somatic nervous system in pediatrics are most commonly related to disturbances in myelination (e.g., Guillain-Barre syndrome).

The autonomic or visceral nervous system consists of the *(1) enteric nervous system*, *(2) sympathetic nervous system*, *and (3) parasympathetic nervous system*.

The *enteric nervous system* consists of:

- *Myenteric plexus of Auerbach*
- *Submucosal plexus of Meissner*

Both plexi are located within the wall of the GI tract and interact with the central (CNS), sympathetic, and parasympathetic nervous systems but also function independently to modulate sensation and peristalsis within the gastrointestinal tract. Developmentally, neurons of the enteric nervous system arise from the same progenitor cell as neurons within the CNS. Consequently, various neurological disorders, such as irritable bowel syndrome, anxiety, and depression, affect both concurrently.

The *sympathetic nervous system* is comprised of myelinated preganglionic and unmyelinated postganglionic fibers. The sympathetic nervous system is frequently referred to as the "thoracolumbar outflow" because preganglionic fibers arise from the thoracolumbar region of the spinal cord. Fibers exit the ventral horn of the spinal cord as ventral roots before separating from the spinal nerves and traveling through the *white communicating rami* and synapsing on the *sympathetic ganglia*. Sympathetic ganglia consist of the *paravertebral* (paravertebral sympathetic chain) and *prevertebral ganglia* that are located adjacent to and distant to the spinal cord respectively. Unmyelinated postganglionic fibers emerge from the paravertebral sympathetic chain and travel through the *gray communicating rami* en route to their target organs. The prevertebral ganglia consist of the *celiac, superior mesenteric, and inferior mesenteric ganglia* that project their unmyelinated fibers toward target organs in the abdomen and pelvis. The primary neurotransmitters of the sympathetic nervous system are acetylcholine and norepinephrine, which are released at the preganglionic and postganglionic synapses respectively. Sweat glands, which receive postganglionic sympathetic fibers releasing acetylcholine, are the exception to this rule (◘ Fig. 22.31).

Spinal cord injuries above the level of T1 may result in hypotension and bradycardia due to the removal of sympathetic innervation.

The sympathetic nervous functions autonomously but is under significant control of descending pathways from the CNS. The role of the sympathetic nervous system is to prepare the body to respond to stress, by triggering an increase in heart rate, pupillary dilation (mydriasis), decreased peristalsis, and stimulation of the adrenal medulla, which releases norepinephrine and epinephrine. Traumatic injury to the spinal cord above T1 causes interruption of these various pathways and results in the loss of sympathetic tone (i.e., bradycardia and hypotension).

The *parasympathetic nervous system* arises from the brainstem and sacral spinal cord and therefore is commonly referred to as the "craniosacral outflow." Like the sympathetic nervous system, the parasympathetic nervous system also consists of preganglionic fibers, parasympathetic ganglia, and postganglionic fibers. Parasympathetic preganglionic fibers arise from the brainstem and sacral spinal cord and travel with cranial nerves (II, VII, IX and X) and sacral splanchnic nerves, respectively. Unlike the sympathetic nervous system, parasympathetic ganglia are in close proximity to target organs and have relatively short postganglionic fibers. Cranial postganglionic fibers via the

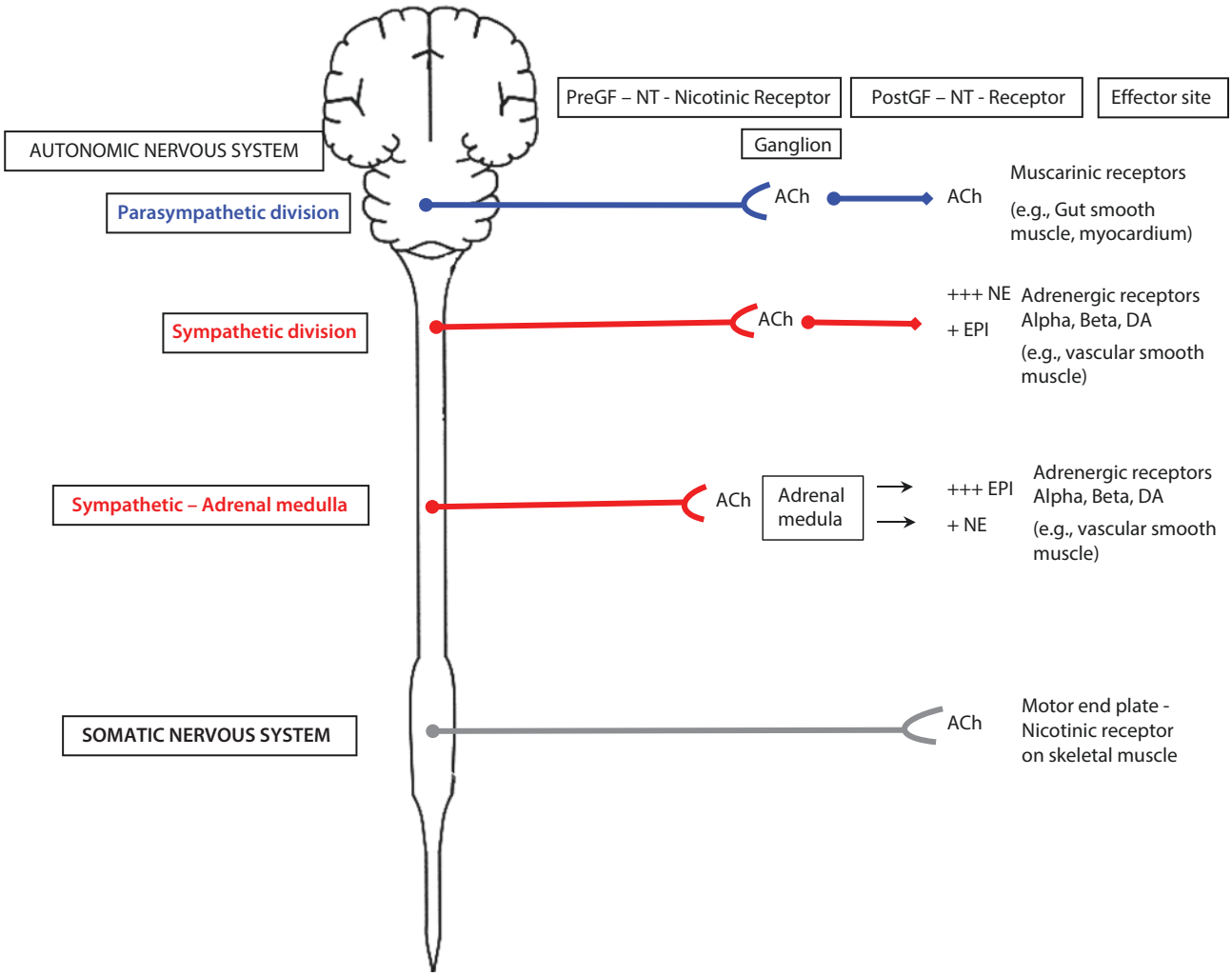


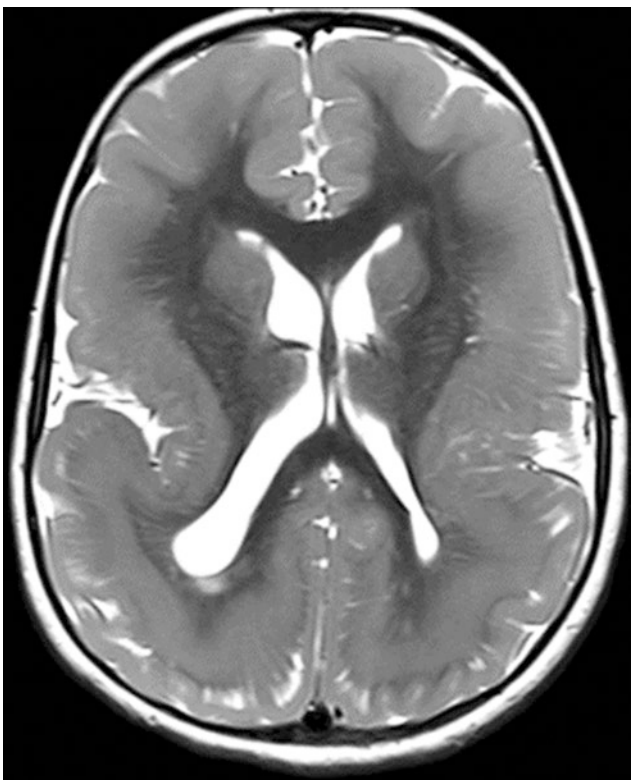
Fig. 22.31 Components of the peripheral nervous system are the autonomic and somatic nervous system. The autonomic nervous system is divided into sympathetic and parasympathetic divisions. Preganglionic fibers (PreGF) arise from the brainstem or spinal cord and synapse at ganglion. Postganglionic (Post-GF) fibers run from the ganglion to effector sites. The main neurotransmitter (NT) of the somatic nervous system is acetylcholine (ACh) whereas Ach and norepinephrine (NE) are the primary neurotransmitters in the autonomic nervous system. Epinephrine (Epi) is the main catecholamine produced by the adrenal medulla, in contrast to sympathetic ganglia, which produce predominantly norepinephrine

celiac ganglia innervate the ciliary muscle, pupillary sphincter, lacrimal glands, salivary glands, and thoracic and lumbar organs. Sacral postganglionic fibers innervate the bladder and genitalia. The parasympathetic nervous system opposes the sympathetic nervous system and produces bradycardia, hypotension, increased gastrointestinal motility, and pupillary constriction. Acetylcholine is the neurotransmitter released from both preganglionic and postganglionic parasympathetic fibers (Fig. 22.31).

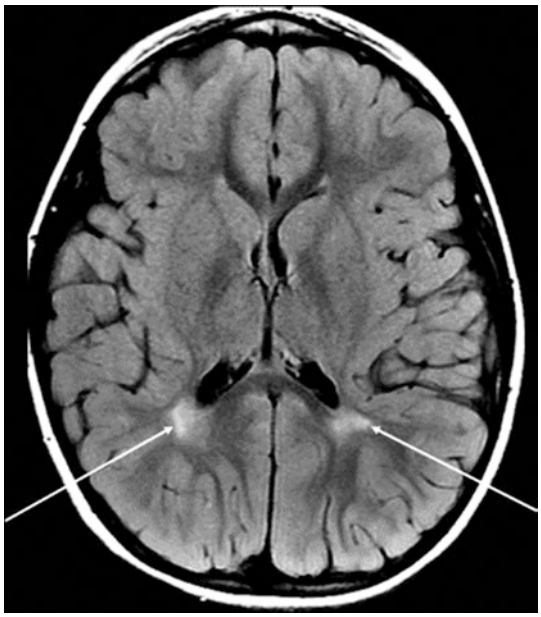
22.4 Summary

Understanding the development, structure, and function of the complex nervous system is essential to caring for critically ill children. Development of the peripheral and central nervous systems is a highly conserved process across a variety of species, which has helped with building on a growing body of knowledge. It is also influenced by a variety of genetic, environmental, molecular, and biochemical factors. Knowledge of the development, structure, and function of the nervous system allows the clinician the opportunity to correlate clinical findings with laboratory and radiographic information to construct a complete clinical picture, which functions as a guide to direct the diagnostic, therapeutic and prognostic approach to children with neurologic insults.

Review Questions

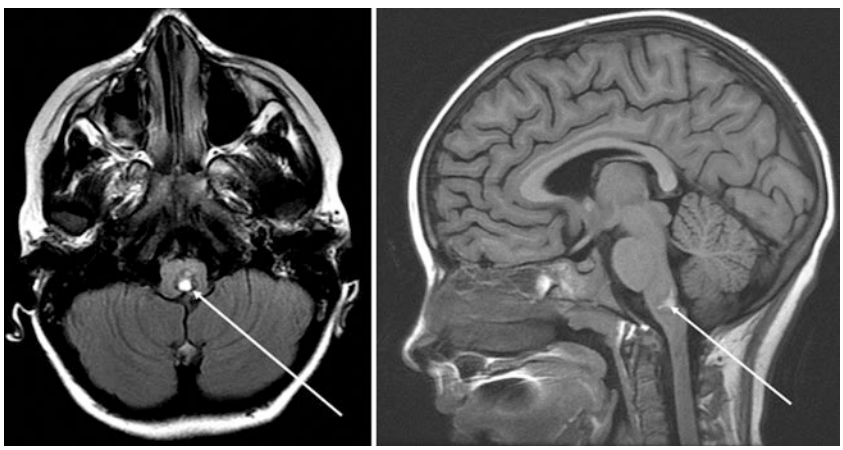


1. The characteristic finding demonstrated in the MRI above is a consequence of genetic and/or environmental stressors impeding normal:
   A. Neurogenesis
   B. Synaptogenesis
   C. Neurulation
   D. Neuronal migration
   E. Apoptosis



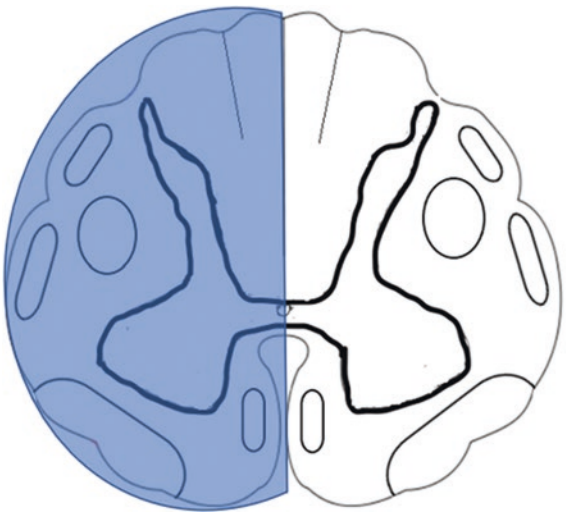
2. The 5-year old female with history of prematurity shown in the MRI above exhibits developmental delay and seizures as a consequence of abnormal:
   A. Myelination
   B. Programmed cell death
   C. Synaptogenesis
   D. Neurogenesis
   E. Neuronal migration

3. Astrocytes play a role in the following except:
   A. Regulation neurotransmitter concentrations at the synaptic junction
   B. Establishment of the blood brain barrier
   C. Regulating of microvascular tone and nutrient blood flow
   D. Development of cerebral edema in response to CNS injury through energy-independent processes

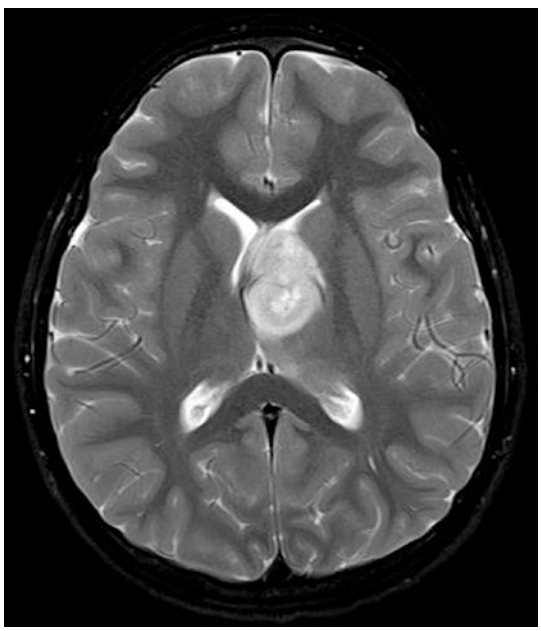


4. Based on the lesion demonstrated in the MRI above, one would most likely expect to see which of the following clinical correlates:
   A. Apnea
   B. Ataxia
   C. Loss of truncal tone

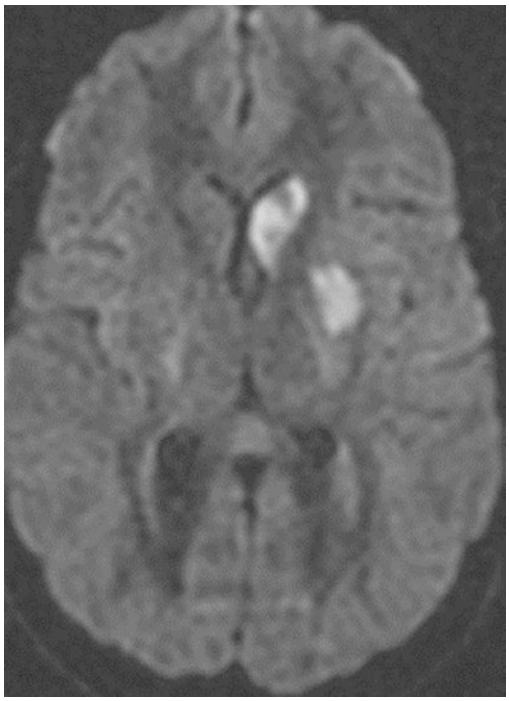
D. Tongue atrophy
E. Upper extremity weakness > lower extremity weakness



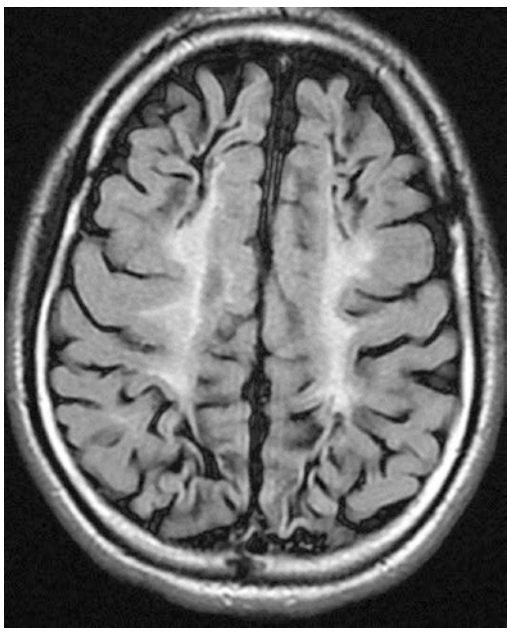
5. Injury to the shaded region of the spinal cord illustrated above will most likely manifest as a loss of:
   A. Contralateral fine touch, pain, temperature, and motor function
   B. Contralateral motor and fine touch; ipsilateral pain and temperature function
   C. Ipsilateral motor and fine touch; contralateral pain and temperature function
   D. Ipsilateral fine touch, pain, temperature, and motor function



6. Based on the location of the lesion above, this patient would most likely present with the following constellation of symptoms except for:
   A. Ataxia
   B. Seizure
   C. Memory loss and confusion
   D. Hemiparesis

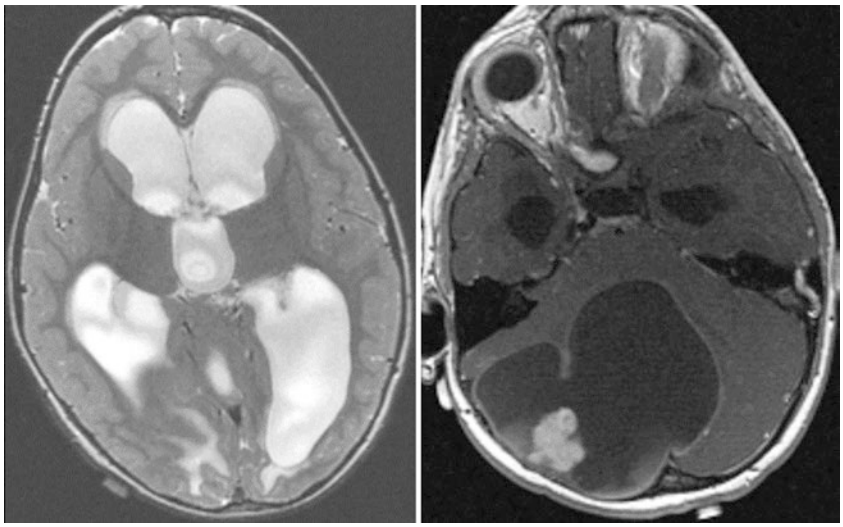


7. Which statement below is true regarding the MRI pictured above?
   A. The patient may have left-sided hemiparesis as a consequence of a left-sided internal carotid artery dissection.
   B. The patient suffered a thromboembolic event involving the right middle cerebral artery.
   C. The lesion is likely to produce obstructive hydrocephalus.
   D. The patient may have right-sided hemiparesis as a consequence of a left-sided internal carotid artery dissection.



8. The 14-year-old depicted in the MRI above developed the findings illustrated as a consequence of:
   A. Cardiac arrest resulting in ischemic injury to watershed areas
   B. Disrupted myelination in utero

C. Right internal carotid dissection
D. Meningitis
E. Shear injury to the bridging veins



9. CSF, as illustrated in the above MRI, has accumulated as a consequence of:
   A. Impaired reabsorption
   B. Obstructed CSF flow
   C. Increased CSF production
   D. The above MRI is normal

Answers

1. D
2. A
3. C
4. D
5. C
6. B
7. D
8. A
9. B

Suggested Readings

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Physiology of Skeletal Muscle and the Neuromuscular Junction

Michael T. Davis and Michael P. Eaton

Contents

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Learning Objectives

The learner should be able to:

- Describe the anatomy and function of the neuromuscular junction and the acetylcholine receptor
- Understand the components of muscle cells responsible for the development of force and its modulation
- Understand the options for inhibition at the neuromuscular junction
- Choose the most appropriate mechanism of NMJ inhibition based on the clinical situation
- Describe abnormalities at the neuromuscular junction pertinent to critically ill children

23.1 Skeletal Muscle

All normal skeletal muscle activity is initiated by nerve impulses.

The 640 or so muscles in the human body are responsible for all voluntary movement, as well as maintenance of posture. Physiologic activity of skeletal muscle is always the result of nerve impulses, transmitted from nerve to muscle at a central area of the muscle fiber called the motor end-plate.

Both cardiac and skeletal muscles are known as striated muscles from their appearance under the microscope. The regular arrangement of contractile elements within the cell, in both the long and short axes of the muscle fiber, is responsible for this appearance, as well as the coordinated function of contraction.

The resting membrane potential of the muscle cell is −95 mV relative to the extracellular environment and is maintained by both potassium and chloride flux.

Like the nerve cells that innervate them, muscle cells use active and passive ion flux across the cell membrane to establish and maintain an electrical gradient between the interior and exterior of the cell. This is termed the resting membrane potential and in muscle cells is due to both potassium (K+) and Chloride (Cl−) ion flux. The resting potential of the myocyte is −95 mV.

23.2 Neuromuscular Junction

The neuromuscular junction is a specialized synapse of the spinal motor neuron and the motor end-plate of the skeletal myocyte. The cell body of the neuron is located in the spinal cord, and the axonal nerve endings arborize to motor end-plates on several different cells within a muscle, forming a motor unit. Because of the presence of the synaptic cleft (approximately 20 nm), a neurotransmitter is required to convey the excitatory impulse to the muscle cell. The neurotransmitter for the neuromuscular junction is acetylcholine. There are various types of acetylcholine receptors in the body, broadly classified as muscarinic and nicotinic due to their agonist response to muscarine and nicotine, respectively. The acetylcholine receptors at the motor end-plate are nicotinic receptors. A schematic depiction of the neuromuscular junction is shown in Fig. 23.1. Except for the extra-ocular muscles, a human adult myocyte has only one neuromuscular junction.

23.2.1 Presynaptic Nerve Terminal

The motor neuron extends from the ventral horn of the spinal cord to the neuromuscular junction via a myelinated axon. At the muscle, it branches to contact numerous muscle fibers. These nerve endings are no longer myelinated but covered by Schwann cells. At the nerve terminal, acetylcholine is produced and released in discrete packets known as quanta. Acetylcholine is produced in the cytoplasm from acetyl coenzyme A and choline in a process catalyzed by cho-

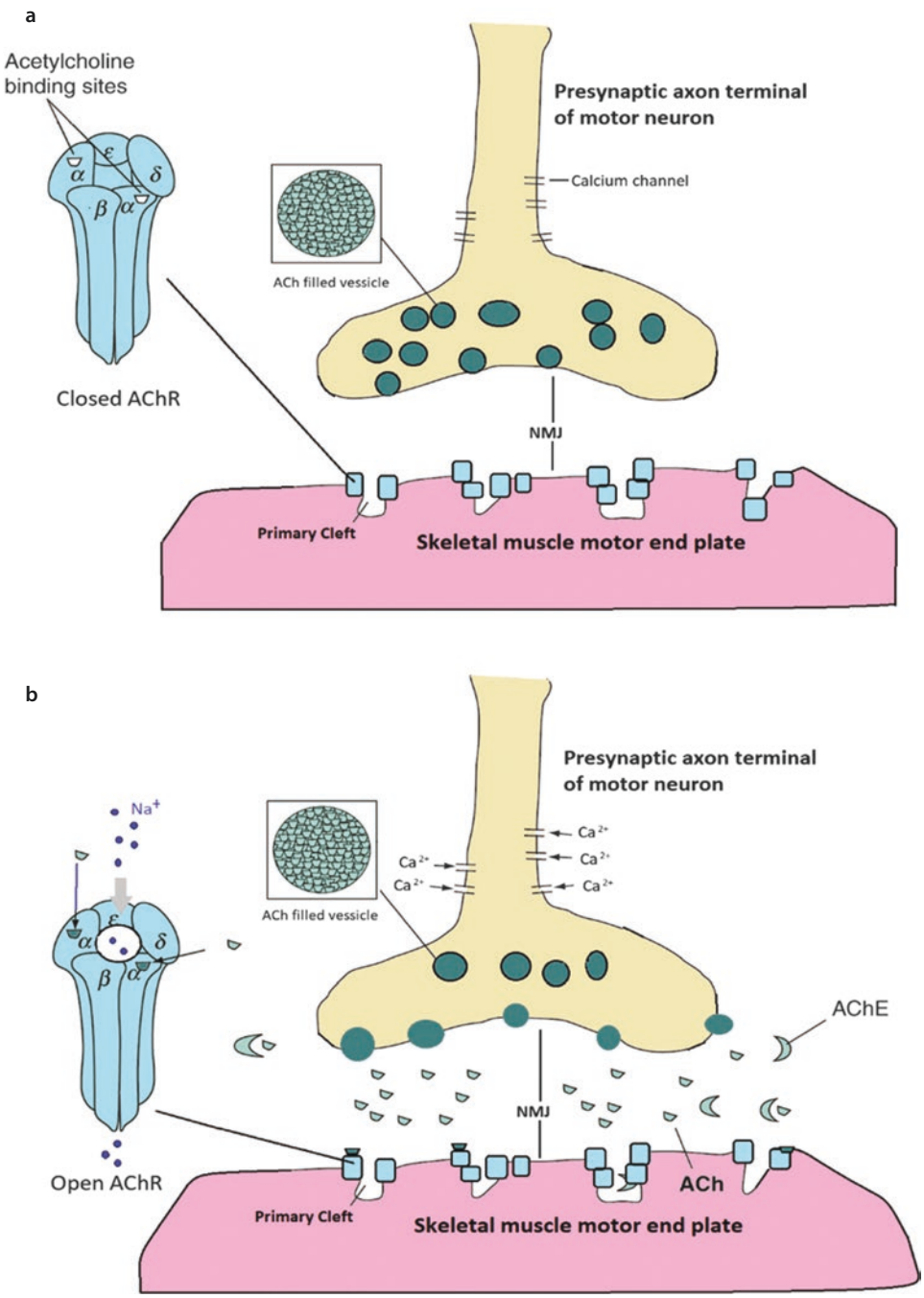


Fig. 23.1 **a** At the nerve terminal, acetylcholine (Ach) is accumulated into vesicles each containing 5000–10,000 molecules of acetylcholine. The vesicles attach in the presynaptic active zone and are primed to respond to a Ca^{2+} signal. **b** With the arrival of an action potential at the nerve terminal, depolarization leads to the opening of voltage-gated Ca^{2+} channels in the cell membrane. The resulting influx of Ca^{2+} causes rapid exocytosis of 200–400 acetylcholine vesicles into the synaptic cleft. The amount of acetylcholine released is related to the amount of Ca^{2+}. ACh-AChR binding results in a conformational change leading to sodium influx through the AChR. Molecules that do not bind to post-synaptic receptors, and those that diffuse away, are rapidly hydrolyzed by acetylcholinesterase. AChR acetylcholine receptor, AChE acetylcholinesterase, NMJ neuromuscular junction

line acetyltransferase. It is then accumulated into vesicles via an energy-dependent process, with each vesicle containing 5000–10,000 molecules of acetylcholine. The vesicles attach in the presynaptic active zone and are primed to become capable of responding to a Ca^{2+} signal. With the arrival of an action potential at the nerve terminal, depolarization leads to the opening of voltage-gated Ca^{2+} channels in the cell membrane. The resulting influx of Ca^{2+} causes rapid exocytosis of 200–400 acetylcholine vesicles into the synaptic cleft. The amount of acetylcholine released is directly related to the amount of Ca^{2+} which enters the nerve terminal, which is in turn related to the external concentration of Ca^{2+}. The opening of voltage-gated and Ca^{2+}-activated K^+ channels likely limits the duration of nerve terminal depolarization.

Acetylcholine is normally rapidly cleared from the neuromuscular junction by acetylcholinesterase.

Acetylcholine molecules that do not bind to post-synaptic receptors, and those that diffuse away, are rapidly hydrolyzed by acetylcholinesterase. The acetylcholine molecules are hydrolyzed into choline and acetate. The choline is taken back up into the nerve terminal for recycling into acetylcholine. The components of the ruptured synaptic vesicles are also recovered and recycled (Fig. 23.1).

23.2.2 Acetylcholine Receptor

Binding of acetylcholine to the nicotinic acetylcholine receptor at the motor end-plate leads to opening of the channel, influx of sodium ions into the myocyte, and generation of an action potential within the myocyte.

The nicotinic acetylcholine receptor is an intrinsic membrane protein which functions as a ligand-gated ion channel. Five subunit proteins (2 α, 1 β, 1 δ, and 1 ε) interact to form a transmembrane pore and binding sites for agonists and antagonists including acetylcholine. There are four membrane-spanning components of each subunit (M1–M4). The predominant negative charge of the M2 regions, which are thought to form the walls of the channel, is postulated to account for the affinity of the receptor for cations. The stable state of this pore is closed, preventing cations from flowing down their electrochemical gradient. The conformational change to the open position requires the *binding of one acetylcholine molecule (or other agonist) to each α subunit simultaneously*, at the junctions with the δ and ε subunits. In the open position, the channel is permeable to cations and a net influx of Na^+ ions occurs. In addition, K^+ ions move out of the cell down their concentration gradient. This creates a depolarization of the end-plate. With sufficient quanta of acetylcholine, the depolarization of the post-synaptic cell causes activation of voltage-gated Na^+ channels outside the end-plate. The opening of these Na^+ channels allows the generation of enough current to produce an action potential in the myocyte.

Acetylcholine receptors are also present at the presynaptic nerve terminal. Agonism at these receptors contributes to a positive feedback mechanism. Antagonism of the nicotinic receptors seems to inhibit this positive feedback.

23.2.3 Muscle Action Potential and Electromechanical Coupling

The influx of Na^+ ions causes the membrane potential to rise from its baseline of −95 mV. If a threshold voltage of −50 mV is reached, an action potential is generated. This requires the activation of 10–20% of the millions of acetylcholine receptors present on each muscle fiber. The action potential generated around the acetylcholine receptor is propagated across the muscle fiber surface and into the transverse tubules (t-tubules). The t-tubules contains many dihydropyridine (DHP) receptors, originally thought to function as calcium channels, but now known to be responsive to voltage changes. As the action potential activates the t-tubule, conformational changes occur in a subunit of the dihydropyridine receptor. DHP receptors serve as voltage sensors and trigger the ryanodine receptor on the sarcoplasmic reticulum to open and release of large amounts of stored Ca^{2+}. Of note, mutations found in the gene encoding ryanodine receptor are pathogenic with affected individuals being at high risk for the development of malignant hyperthermia.

Transmission of the myocyte action potential leads to the opening of voltage-gated Ca^{2+} channels in the sarcoplasmic reticulum. This calcium binds to troponin, allowing the interaction of actin and myosin. This is the mechanism of electromechanical coupling.

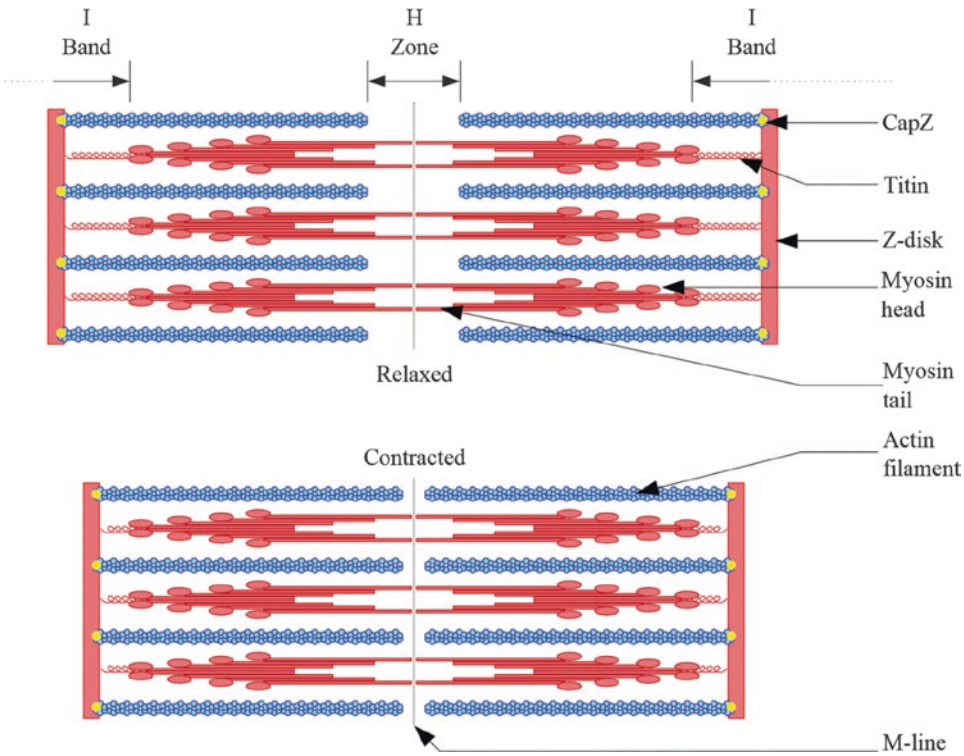
23.3 Contractile Apparatus and Development of Muscle Tension

The actual work of muscular contraction is accomplished through the interaction of actin and myosin. Actin (thin filaments) and myosin (thick filaments) are arranged linearly side by side and overlapping lengthwise into a functional unit called the sarcomere, with 6 actin filaments surrounding each myosin filament (■ Fig. 23.2). Myosin filaments terminate in a globular "head" which is oriented toward the neighboring actin. At rest, the myosin heads are prevented from interacting with actin by tropomyosin and the troponin complex. Ca^{2+} released from the SR binds to the troponin C, causing the release of tropomyosin and allowing interaction between actin and myosin, producing mechanical contraction. The myosin head then binds to the actin filament and flexes, moving the thick and thin filaments relative to one another, shortening the sarcomere. This ratcheting movement can repeat if the calcium concentration remains high and adequate energy is available in the form of ATP. Contraction is terminated when Ca^{2+} is pumped back into the sarcoplasmic reticulum by a Ca^{2+}-ATPase. Thus, both contraction and relaxation are energy-dependent processes. Additionally, as the sodium channels close, chloride channels open and the resultant anion flux returns the myocyte membrane to its resting potential. Sodium and chloride ions are then pumped across the membrane against their concentration gradients to re-establish the baseline concentrations.

The individually tiny movements of the actin-myosin interactions within each sarcomere are combined with other sarcomeres connected end to end throughout the muscle, and with surrounding muscle fibers. The muscle fibers innervated by a single motor neuron and the neuron itself are called a motor unit. Motor units of different sizes exist within individual muscles, varying from <10 to several hundred fibers. Recruitment of multiple motor units to meet a demand for increased force proceeds from smaller to larger units.

Actin-myosin interactions are inhibited at rest by the troponin complex (troponin I) and tropomyosin. Calcium-mediated disinhibition causes contraction.

Both muscle contraction and muscle relaxation are active processes that require energy in the form of ATP.



■ **Fig. 23.2** Sarcomere demonstrating actin-myosin interactions in the relaxed and contracted states. (► https://commons.wikimedia.org/w/index.php?curid=2264027)

Temporal summation of fiber contractions also contributes to muscle force development if continued stimuli are transmitted by the motor neuron. Temporal summation of developed tension achieves a peak at a stimulus frequency of 50 stimuli per second (50 Hz).

23.3.1 Energy Requirements and Limitations

Energy requirements for muscle activity can be met with intracellular stores for only very short periods of time. Anaerobic glycolysis and lactic acid accumulation limit prolonged vigorous activity.

The development of significant force in a contracting muscle requires large amounts of energy in the form of ATP. ATP stores within myocytes can sustain only very brief (<1 s) activity. High-energy phosphates are also stored in muscle as creatine phosphate. Creatine phosphate is converted to ATP by creatine kinase. Creatine phosphate increases immediately available energy for contraction only marginally, and ongoing activity requires generation of additional ATP through aerobic glycolysis. Limitations in oxygen delivery result in a necessity for anaerobic glycolysis for extended muscle work, which is far less efficient and produces lactic acid, buildup of which eventually limits continued activity.

23.4 Neuromuscular Function in the Newborn

Neuromuscular function remains immature in the newborn until 2–3 months of age. During this period, there remain fetal-type acetylcholine receptors, which contain a δ-subunit instead of the ε-subunit. These fetal-type acetylcholine receptors have decreased conductance to cations as compared to the mature type. Newborns are more susceptible to muscle fatigue with stimulation. In addition, they also exhibit variable reactions to muscle relaxants because of differences between the infant and the adult in the neuromuscular junction, the volume of drug distribution, and the fiber-type distribution.

23.5 Inhibition at the Neuromuscular Junction

Neuromuscular blockade is discussed extensively in ▶ Chap. 28. However, a clear understanding of the physiology of this process is essential for the appropriate use of these medications. Neuromuscular blockers can be categorized as competitive or non-competitive, or as non-depolarizing and depolarizing. Commonly used non-depolarizing neuromuscular blockers function according to a competitive blockade, whereas the clinically applicable depolarizing neuromuscular blockers interact by a non-competitive mechanism.

23.5.1 Non-depolarizing Neuromuscular Blockers

Muscle relaxants are cations containing quaternary nitrogen atoms. Molecules of non-depolarizing muscle relaxants bind one or both acetylcholine receptor-binding sites both at the presynaptic nerve terminal and the motor end-plate. This prevents the conformational change required to open the channel which occurs when both binding sites are occupied by agonists. Although both sites must be bound by acetylcholine in order to open the channel, only one site needs to be occupied by an antagonist to prevent channel opening. Thus, the degree of inhibition is highly dependent on the ratio of concentrations of acetylcholine and antagonist.

Reversal of neuromuscular blockade may be accomplished by the administration of an acetylcholinesterase inhibitor (e.g., neostigmine). When a reversal agent is administered, the inhibition of acetylcholinesterase results in an increased concentration of acetylcholine in the NMJ. The increased concentration allows increased binding to acetylcholine receptors and cause activation. Reversal of the competitive blockade will be more effective when lower concentrations of antagonist are present.

Neuromuscular blockers are eventually cleared by diffusion away from the neuromuscular junction and metabolism by the liver, kidney, or blood. Acetylcholinesterase inhibitors are not site specific and cause increased concentration of acetylcholine at all receptor sites, including muscarinic receptors. *Thus, a muscarinic receptor antagonist, such as glycopyrrolate or atropine, must be given concurrently with the reversal agent to prevent unwanted parasympathetic activity*.

Acetylcholinesterase inhibitors are not site specific and cause increased concentration of acetylcholine at all receptor sites, including muscarinic receptors. A muscarinic receptor antagonist, such as glycopyrrolate or atropine, must be given concurrently with the reversal agent to prevent unwanted parasympathetic activity.

The neuromuscular blockade by rocuronium and vecuronium can also be reversed by sugammadex. Sugammadex selectively binds (encapsulates) aminosteroid neuromuscular blocking agents (NMBAs). Affinity is greatest for rocuronium, followed in decreasing by vecuronium, and pancuronium. Sugammadex has no effect on succinylcholine or the benzylisoquinolinium NMBAs (e.g., atracurium, cisatracurium, mivacurium). Once sugammadex forms a complex with the aminosteroid NMBA, it reduces the amount of neuromuscular blocking agent available to bind with the acetylcholine receptor at the neuromuscular junction. As a result, neuromuscular blockade is reversed. Sugammadex has less hemodynamic effects than neostigmine and does not require the use of glycopyrrolate or atropine.

23.5.2 Depolarizing Neuromuscular Blockers

The only available depolarizing neuromuscular blocking agent in the United States is succinylcholine. This agent binds both α-subunits, and initially simulates the effects of acetylcholine. When it binds to the receptors at the motor end-plate and the presynaptic nerve terminal, the channels are opened, and the end-plate depolarizes. This produces an initial series of disorganized muscle contractions called fasciculations. However, because it is not hydrolyzed by acetylcholinesterase, it remains in the cleft until it is cleared by diffusion into the plasma where it is hydrolyzed by plasma cholinesterase. Thus, although the molecules detach from the receptor nearly as quickly as acetylcholine (approximately in 1 ms), they immediately react with another receptor such that the end-plate is continuously depolarized. This causes the voltage-gated sodium channels described above to remain in an inactive condition rather than returning to their resting state. Although the acetylcholine receptors are continuously activated, the muscle cannot contract after the initial fasciculations.

23.5.3 Other Non-competitive Inhibition of the Neuromuscular Junction

Transmission through the acetylcholine receptor may also be influenced by mechanisms that change receptor function without affecting the receptor-binding site. These mechanisms alter the dynamic function of the receptor. For example, the speed with which channels open and close following receptor binding may be altered. The three most common mechanisms by which this occurs includes receptor desensitization, channel blockade, and the phase II block classically associated with succinylcholine. These categories all include a wide range of mechanisms which can interfere with the normal function of this very large and complex receptor.

Desensitization occurs when conformational change of various portions of the subunits maintains the receptor in an inactive state such that attachment of an agonist does not lead to opening of the channel. These conformational changes may result from the binding of moieties or a change in the environment of the receptor. Agents that can promote this state include volatile anesthetics, antibiotics, local anesthetics, alcohols, cocaine, barbiturates, phenothiazines, and receptor agonists.

Channel-blocking medications such as local anesthetics and Ca^{2+}channel blockers can inhibit the flow of ions (e.g., calcium, sodium) through their respective channels throughout the body. This inhibition of ion flow may also occur at the level of the acetylcholine receptor. This block of ion flow may occur in either the open or closed position. In the closed position, medications block the opening of the channel and prevent the flow of ions such that they do not reach the end-plate and depolarization does not occur. The open position is a use-dependent inhibition in that it occurs only when the channel has been opened by receptor binding in the face of incomplete penetration down to the end-plate. In either form, the normal flow of ions through the receptor channel is impeded, depolarization of the end-plate is prevented, and the neuromuscular transmission is blunted or blocked. However, because receptor site binding is not the etiology of the impaired transmission, acetylcholinesterase inhibitors will not be effective in reversing the problem. In fact, it has been suggested that acetylcholinesterase inhibitors may serve as channel-blocking drugs. Other medications that may be associated with channel block at the neuromuscular junction include antibiotics (especially aminoglycosides and clindamycin), cocaine, tricyclic antidepressants, naltrexone, and naloxone.

23.6 Sensitivity to Neuromuscular Blockade

Muscle groups have varying sensitivities to neuromuscular blockers.

Muscle groups have varying sensitivities to neuromuscular blockers. As a result, the observation that one muscle is paralyzed, or has recovered from paralysis, cannot necessarily be generalized to all muscle groups. In older infants and adults, the diaphragm and the larynx are quite resistant to neuromuscular blockade compared to the most commonly used monitoring site, the adductor pollicis muscle. Conversely, the upper airway muscles and the masseter muscle are quite sensitive to neuromuscular antagonists. Thus, knowledge of the relative sensitivity of the monitoring site must be considered with respect to the muscle group of interest. Additionally, as described above, there is a maturation process of neuromuscular transmission which seems to be completed around 2 months of age. In the intensive care unit, complete paralysis is rarely necessary, and complete recovery is usually expected before considering extubation, such that application of any of the commonly used monitoring sites should suffice.

23.7 Abnormalities of Skeletal Muscle and the Neuromuscular Junction

Conditions such as denervation injuries, burns, major trauma, immobility, and intracranial disorders can lead to the proliferation of acetylcholine receptors in children. This proliferation of receptors makes the patient more sensitive to the depolarizing neuromuscular blockers (and all the potential adverse effects, especially hyperkalemia), and less sensitive to the non-depolarizing agents.

There are some disease states which have enhanced the understanding of the physiology of the neuromuscular junction. Moreover, there are also some disease states that impact the safety and effectiveness of neuromuscular blocker use. Most of the diseases which are directly related to the neuromuscular junction, such as myasthenia gravis and Eaton-Lambert syndrome, are rare in the pediatric population. Myasthenia gravis is caused by antibodies to the acetylcholine receptor at the neuromuscular junction, and is characterized by rapid

fatigue of muscles, demonstrated by inability to perform such tasks as sustained upward gaze or sustained head lift. Children with myasthenia gravis will be exquisitely sensitive to neuromuscular blockers. The Eaton-Lambert syndrome is also an immune-mediated disorder of neuromuscular transmission associated with muscle weakness. In contrast to myasthenia gravis, however, it is associated with impaired release of acetylcholine as autoantibodies are formed against the presynaptic voltage-gated calcium channels. In this syndrome, there tends to be improved muscle function with activity as the result of accumulation of presynaptic calcium and improved release of acetylcholine.

Conditions which can lead to the proliferation of acetylcholine receptors are not uncommon in children. Such conditions include denervation injuries, burns, major trauma, immobility, and intracranial disorders. A decrease in acetylcholine release or prolonged inhibition can lead to increased acetylcholine receptor density at the motor end-plate. In addition, severe injury can also lead to the proliferation of extra-junctional acetylcholine receptors found along the muscle membrane. This proliferation of receptors makes the child more sensitive to the depolarizing neuromuscular blockers (and all of the potential adverse effects, especially hyperkalemia), and less sensitive to the non-depolarizing agents. This proliferation of receptors is evident within several hours of lower motor neuron injury, and the effects last for at least several months. The onset of these effects after upper motor neuron injury is somewhat slower, and high risk has been documented out to 6 months.

The muscular dystrophies may also lead to abnormalities in the acetylcholine receptors. Although innervations are relatively normal in these conditions, post-synaptic acetylcholine receptors are a mixture of fetal- and adult-type receptors. The preponderance of fetal acetylcholine receptors in the dystrophic muscle likely represents the effect of muscle regeneration rather than dystrophic muscle. Although fetal-type receptors are less sensitive to neuromuscular blocking agents than the adult-type, the patient response to blockade and reversal is unpredictable. In fact, patients with muscular dystrophy may be unusually sensitive to non-depolarizing agents. Finally, hyperkalemia and cardiac arrest have been clearly documented following succinylcholine administration in patients with undiagnosed muscular dystrophies.

Review Questions

1. Which of the following statements is true regarding the membrane potential of skeletal muscle cells?
   A. The resting potential is +95 mV.
   B. The resting potential is due exclusively to potassium current.
   C. The resting potential is due exclusively to chloride current.
   D. Depolarization to a potential of −50 mV results in an action potential.
   E. The resting potential is maintained throughout the action potential.

2. Transmission through the acetylcholine receptor may be influenced by mechanisms that change receptor function without affecting the receptor-binding site. The three most common mechanisms by which this occurs include receptor desensitization, channel blockade, and succinylcholine phase II block. Which of the following most accurately describes the process of desensitization?
   A. Desensitization occurs at neuromuscular junctions continuously in contact with depolarizing agents when the membrane potential returns to normal, but the depolarizing agent is still present.
   B. Desensitization occurs when a conformational change within the acetylcholine receptor subunits maintains the receptor in an inactive state such that attachment of an agonist does not lead to opening of the channel.

C. Desensitization only occurs when both sites of the acetylcholine receptor are bound by neuromuscular antagonists.
D. Desensitization results from a structural change in the acetylcholine receptor subunits but does not alter the dynamic function of the receptor.
E. Desensitization results from the inhibition of the flow of ions at the level of the acetylcholine receptor by a variety of medications at dosages clinically used.

3. Which of the following is true regarding the development of tension in skeletal muscle?
A. The calcium that binds troponin c during contraction is mostly from extracellular sources.
B. Activation of the ryanodine receptor causes release of calcium from the sarcoplasmic reticulum.
C. Calcium binds tropomyosin, activating actin-myosin binding.
D. Contraction is terminated due to the passive diffusion of calcium into the sarcoplasmic reticulum.
E. The motor unit is composed of a single sarcomere and its innervating motor neuron.

4. Which of the following statements is true regarding the neuromuscular junction (NMJ)?
A. The NMJ consists of the presynaptic nerve terminal, the synaptic cleft, and the motor end-plate.
B. Motor neuron electrical impulses are directly communicated to the muscle cell without the need for a neurotransmitter.
C. Acetylcholine is synthesized in the synaptic cleft by combining acetate and choline.
D. Myasthenia gravis is caused by a defect in the gene coding for acetylcholine receptor subunits.
E. Acetylcholine is cleared from the NMJ by pseudocholinesterase.

5. A 16-year-old male with a spinal cord injury is being re-admitted to the pediatric intensive care unit from the rehabilitation unit for intubation and mechanical ventilation secondary to nosocomial pneumonia. In preparing for the intubation, the bedside nurse asks if you would like her to draw up succinylcholine. Which of the following would be your best response to his suggestion?
A. Denervation injuries can lead to an increased acetylcholine receptor density at the motor end-plate, and thus, twice the dose of succinylcholine will be needed.
B. Denervation injuries can lead to an increased acetylcholine receptor density at the motor end-plate, but only after years of decreased acetylcholine release or prolonged inhibition, and thus, the usual dose of succinylcholine may be administered.
C. Denervation injuries can lead to an increased acetylcholine receptor density at the motor end-plate, making the adolescent more sensitive to the effects of succinylcholine, and thus, its use should be avoided.
D. Denervation injuries can result in a decrease in acetylcholine receptor density at the motor end-plate, and thus, only half the dose of succinylcholine will be required.
E. Denervation injuries should not affect the acetylcholine receptor density at the motor end-plate, and thus, the usual dose of succinylcholine may be administered.

Answers

1. D
2. B
3. B
4. A
5. C

1. The resting membrane potential of a muscle cell is approximately −95 mV and is maintained by both potassium and chloride currents. Depolarization of the membrane to a potential of −50 mV by influx of sodium ions causes an action potential. Transmembrane potentials change rapidly during an action potential, and the resting potential is restored only after the action potential is terminated.
2. Desensitization occurs when a conformational change within the acetylcholine receptor subunits maintains the receptor in an inactive state such that attachment of an agonist does not lead to opening of the channel. Phase II block occurs at neuromuscular junctions continuously in contact with depolarizing agents when the membrane potential returns to normal, but the depolarizing agent is still present. Desensitization results from a structural change in the acetylcholine receptor subunits but does not alter the dynamic function of the receptor. Inhibition of the flow of ions at the level of the acetylcholine receptor can be caused by channel-blocking medications such as local anesthetics and Ca^{2+}–channel blockers at dosages clinically used.
3. The calcium source for excitation-contraction coupling in muscle cells is from the sarcoplasmic reticulum. Activation of the ryanodine receptor on the SR is responsible for this calcium release. Calcium then binds to troponin c, releasing tropomyosin from actin and allowing actin-myosin interactions. Termination of contraction requires calcium ATPase in an energy-requiring process. The motor unit consists of a motor neuron and all muscle fibers it innervates.
4. The neuromuscular junction consists of the presynaptic nerve terminal, the synaptic cleft and the motor end-plate of the muscle cell. The synaptic cleft creates a requirement for a neurotransmitter to bridge the gap. Acetylcholine is synthesized in the neuronal cytoplasm from acetyl-CoA and choline and broken down in the synaptic cleft by acetylcholinesterase (true cholinesterase) to acetate and choline.
5. Denervation injuries can lead to an increased acetylcholine receptor density at the motor end-plate, making the adolescent more sensitive to the effects of succinylcholine, and thus, its use should be avoided. Severe injury can also lead to the proliferation of extrajunctional acetylcholine receptors found along the muscle membrane. This proliferation of receptors makes the patient more sensitive to the depolarizing neuromuscular blockers (and all of the potential adverse effects, especially hyperkalemia), and less sensitive to the non-depolarizing agents. This proliferation of receptors is evident within several hours of lower motor neuron injury, and the effects last for at least several months. The onset of these effects after upper motor neuron injury is somewhat slower, and high risk has been documented out to 6 months.

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Assessment of Neurologic Function

Elizabeth E. Scarlett and Jill M. Gotoff

Contents

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24

Learning Objectives

- Describe examination techniques important in the assessment of neurologic function.
  - Include cortical, brain stem, and spinal examinations of the child with altered mental status or acute neurologic deficit.
- Differentiate upper motor neuron pathology from lower motor neuron pathology.
- Understand the utility and limitations of the Glasgow coma scale.
- Appreciate the presentation of common peripheral nerve lesions.
- Describe findings in herniation syndromes.
- Describe spinal syndromes and their unique physical examination findings.
- Delineate the components of a brain death examination.
- Describe the technique, clinical applications, and limitations of intracranial pressure monitoring in the child with intracranial hypertension.
- Understand the differences between intracranial monitoring devices.
- Understand indications, contraindications, and analysis of cerebrospinal fluid and opening pressure measurement.
- Understand the indications for the use of electroencephalography and evoked potentials in the neurologically compromised child.
- Review indications and limitations of neuroimaging techniques.
- Explore the potential role biomarkers have in guiding management of the neurocritically ill child.

24.1 Introduction

The most important component of neurologic assessment of the patient in the PICU is serial evaluation of level of consciousness.

Despite multiple advances in neuroimaging, monitoring of intracranial hemodynamics, and electrodiagnosis, serial neurological examinations remain the primary method to detect clinical changes in the child with potential or ongoing neurologic impairment. Neurologic dysfunction must be discriminated from sedation, residual anesthesia, neuromuscular blockade, and psychological adjustment to the pediatric intensive care unit (PICU) environment. Toxins, infections, metabolic diseases, and hypoxia tend to cause generalized cerebral dysfunction with relative sparing of the brainstem structures. Tumors, trauma, and focal ischemia tend to cause localized lesions that can manifest as neurologic dysfunction involving the specific areas of the cerebral hemispheres, brainstem, or both.

This chapter will explore the various modalities for the neurologic assessment of the critically ill pediatric patient using physical examination, intracranial pressure (ICP) monitoring, cerebral spinal fluid (CSF) analysis, neurophysiologic monitoring, imaging modalities, and biomarkers.

24.2 Examination

Neurological assessment of the critically ill child requires systematic, thorough serial examinations to detect new or progressive abnormalities in central or peripheral neurologic function. Each examination begins with observation of the level of consciousness and progresses through a precise evaluation of neurologic integrity. The examination will be described in the context of neuroanatomy; beginning with an assessment of cortical function, followed by brainstem, spinal cord, and the neuromuscular junction.

24.2.1 Consciousness

Consciousness refers to the awareness of self and environment. Coma is the absence of awareness of self and environment, even with external stimulation. Consciousness depends on intact functioning of the cerebral cortices and the ascending reticular activating system, components of which are found in the medulla, pons, and thalamus. Severe derangements at any of these anatomic sites can cause alteration of consciousness. These derangements can be biochemical (e.g. poisonings), structural (e.g. trauma), or functional (e.g. status epilepticus) and occur either singly or in combination.

Between normal consciousness and coma are a variety of altered states of responsiveness. Levels of consciousness are assessed by inspection and response to verbal and painful stimuli (Table 24.1). A child who is upset and appears restless, whose eyes are open and looking about the room, has a normal mental state or at worst a mildly altered sensorium. Sleepiness during periods in which wakefulness is expected may indicate a minimal degree of altered responsiveness.

Table 24.1 Glasgow coma scale

	Infant < 1 year	Child 1–4 years	Age 4-Adult	Score
Eye opening (E)	Open	Open	Open	4
	To voice	To voice	To voice	3
	To pain	To pain	To pain	2
	No response	No response	No response	1
Verbal response (V)	Coos, babbles	Oriented, speaks, interacts, social	Oriented and alert	5
	Irritable cry, consolable	Confused speech, disoriented, consolable	Disoriented	4
	Cries persistently to pain	Inappropriate words, inconsolable	Nonsensical speech	3
	Moans to pain	Incomprehensible, agitated	Moans, unintelligible	2
	No response	No response	No response	1
Motor response (M)	Normal, spontaneous movements	Normal, spontaneous movements	Follows commands	6
	Withdraws to touch	Localizes pain	Localizes pain	5
	Withdraws to pain	Withdraws to pain	Withdraws to pain	4
	Decorticate flexion	Decorticate flexion	Decorticate flexion	3
	Decerebrate extension	Decerebrate extension	Decerebrate extension	2
	No response	No response	No response	1
Total score equals eye + verbal + motor scores. Maximum score is 15				

Examples of progressively altered states commonly seen in the PICU include:

- *Somnolence*: The patient is sleepy but arouses to an awake state and sensorium is intact.
- *Hypersomnolence*: Arouses to stimulation but drifts off to sleep inappropriately.
- *Stupor*: Appears asleep, arouses to vigorous stimulation, but sensorium is clouded.
- *Light coma*: No response to verbal stimuli, may withdraw to pain, reflexes are intact, and breathing is adequate.
- *Coma*: No spontaneous movements, absent reflexes, breathing may be impaired.

The Glasgow Coma Score Scale can be used to quantify the depth of coma.

Examiners often need to quantify the "depth" of coma and have traditionally used the Glasgow Coma Scale (GCS) score to do so. The GCS was first described in adult trauma patients but has been modified for use in infants and children. This scale uses the summation of scores of three easily observable responses (eye opening, verbalization, motor) to derive a numerical score from 3 to 15 (◘ Table 24.1).

The scoring system was derived for adult patients with traumatic brain injury and has some population-based prognostic value for that group. Patients with head trauma who have a GCS of 8 or less are categorized as having sustained severe brain injury and have a worse prognosis than those with a GCS of 9–13 (moderate head injury). Although the GCS is easily defined and widely understood in describing patients with traumatic coma, it has limited prognostic implications for nontraumatic coma.

Mild traumatic brain injury (TBI) is defined as a GCS of 14–15; moderate TBI is defined as a GCS of 9–13; and severe TBI is defined as GCS of 3–8.

Caution should be taken in obtaining GCS scores in patients who are chemically sedated. To obtain the most accurate GCS score and neurologic examination, temporarily discontinue all sedating medications. It is helpful to perform a "nonsedated" thorough neurologic exam with collaborating teams (neurosurgery, neurology, PICU team) when applicable to ensure consistency. Scores should be documented not only as a total number, but include the number for each individual section, for example: E3 M4 V5 = GCS 12. A verbal response cannot be accurately obtained in an intubated patient; therefore, the V score is replaced with a T1. The above exam then becomes: E3 M4 VT1 = GCS 8 T. Growing evidence suggests that the motor component of the GCS is as reliable a predictor of outcome as the full GCS score. Additionally, in children the motor score alone is easier and faster and eliminates the conundrum of scoring the intubated patient.

24.2.2 Brainstem

Whereas the function of the cerebral hemispheres is primarily assessed by determining the level of consciousness, brainstem activity is assessed by the systematic evaluation of the cranial nerves, respiratory patterns, and hemodynamic responses to internal and external stimuli.

24.2.2.1 Cranial Nerve Exam

The cranial nerves provide both motor and sensory functions and may be difficult to assess in the intubated and poorly responsive patient. In the child unable to cooperate with a full examination, cranial nerve (CN) evaluation focuses mainly on the assessment of the pupillary response to light, the corneal reflex, caloric testing of vestibular function, facial symmetry, and the gag reflex

Table 24.2 Cranial nerves

Cranial nerve		Function
I	Olfactory nerve	Smell
II	Optic nerve	Visual acuity, visual fields, afferent pupillary response to light
III	Oculomotor	Extraocular movement up and down, efferent pupillary response to light, ability to lift eyelids
IV	Trochlear	Eye movement downward and inward
V	Trigeminal nerve	Masseters, pterygoids, facial sensation, afferent corneal reflex
VI	Abducens nerves	Eye movement outward
VII	Facial nerve	Orbicularis oris, oculi, frontalis, efferent corneal reflex, taste (anterior 2/3 of tongue)
VIII	Acoustic nerve	Hearing, vestibular responses
IX	Glossopharyngeal nerve	Elevation of palate, afferent gag reflex
X	Vagus nerve	Swallowing, movement of vocal cords, efferent gag reflex
XI	Spinal accessory nerve	Sternocleidomastoid, trapezius function
XII	Hypoglossal nerve	Tongue movement, fasciculations

(Table 24.2). The relevant anatomic correlates and proper techniques for testing these reflex arcs are described in Table 24.2.

Pupillary Light Response

The normal pupillary response to light exposure is bilateral constriction and depends on intact afferent and efferent pathways. Impulses from each eye are carried by the respective optic nerves. At the optic chiasm, the two optic nerves meet and decussate with the fibers from the lateral retina remaining on the same side and the fibers from the medial retina crossing. From this point, the neurons involved in the light reflex travel along the optic tract, synapsing in the pretectal nuclei of the midbrain close to the midline. Axons from these nuclei project bilaterally to the Edinger-Westphal nuclei with fibers crossing both through the posterior commissure and ventral to the aqueduct. Efferent fibers from each Edinger-Westphal nucleus are carried to the pupillary sphincter muscles of the ipsilateral eye via the oculomotor nerve (CN III).

A full understanding of this pathway allows localization of pathology involving the pupillary light reflex arc (Table 24.3). Lesions of the eye and optic nerve (CN II) will affect the reflex bilaterally (neither pupil will constrict) when a light is directed toward the affected eye. Similarly, midline lesions within the optic chiasm do not affect the pupillary light response until relatively late in their course since the neurons associated with the reflex are carried laterally within the optic nerve. Lesions that affect the midbrain (e.g., central herniation) usually affect the pretectal and/or Edinger-Westphal nuclei bilaterally and thus affect the pupillary light reflex bilaterally. Finally, lesions of the oculomotor nerve (CN III) itself lead to ipsilateral pupillary dilation or dysfunction on the affected side.

Table 24.3 Pathologic alterations of the pupillary light reflex

Site of lesion	Response to light
Retina, prechiasm CN II	No response bilaterally when light directed toward ipsilateral eye, constriction bilaterally when light directed toward unaffected eye
Symmetric brainstem process	No response bilaterally
Isolated CN III	No constriction of ipsilateral eye when light directed toward either eye

Table 24.4 Pathologic alteration of the corneal reflex

Site of lesion	Response to corneal stimulation
Ophthalmic branch of CN V (V1)	No response bilaterally when affected eye is touched
	Normal response when unaffected eye is touched
Pons	No response bilaterally
Motor nucleus of CN VII or peripheral nerve of CN VII	No blink on affected side to stimulation bilaterally

Corneal Reflex

The normal corneal reflex causes closure of both eyes when a light touch (e.g. cotton wisp, saline drop) is applied to one cornea. The reflex arc includes the sensory fibers of the cornea that travel in the ophthalmic branch of the trigeminal nerve (V1 of CN V) and end in the ipsilateral sensory nucleus of the trigeminal nerve in the pons. Neurons then project to both motor nuclei of the facial nerve (CN VII) also located in the pons. From this nucleus, the facial nerve travels to the ipsilateral orbicularis oculi muscle. The blink reflex in the contralateral eye is augmented by the actions of cortical projections and may be diminished or absent in patients with marked acute cortical dysfunction.

Lesions of V1 of CN V will cause loss of both the ipsilateral and contralateral blink responses, as will lesions of the ipsilateral sensory nucleus of CN V. Lesions of the pons at the level of the sensory nucleus of CN V and motor nucleus of CN VII will cause loss of the entire corneal reflex bilaterally. Finally, lesions specific to the motor nucleus of CN VII or along the pathway of CN VII itself will cause failure of the reflex on the ipsilateral side of pathology (Table 24.4).

Eye Movements

Examination of the neurologically impaired patient "at rest" often demonstrates slow random eye movements that may be conjugate or dysconjugate. These movements are often associated with the presence of intact caloric responses. The quality of the responses does not have any independent prognostic significance. Since nystagmus is almost never seen in coma because it is mediated by higher cortical centers, the following discussion focuses on the slow (tonic) component of these reflex eye movements.

In the comatose patient, the reflex pathway encompassing the acoustic nerve (CN VIII) and the motor nerves of the eye (oculomotor nerve; CN III, trochlear nerve; CN IV, abducens nerve; CN VI) can be tested using either a proprioceptive stimulus (e.g., head turning or doll's eyes reflex) or a direct vestibular stimulus (caloric testing – usually done with ice water instillation in external auditory canal). In order to facilitate understanding of the relevant anatomic correlates of the vestibular-ocular reflexes, both will be discussed. Although for clinical purposes, caloric testing is usually preferred for the comatose PICU patient.

The *doll's eyes reflex* (oculocephalic reflex) is elicited by turning the head briskly from midline to one side, first in the horizontal plane and then in the vertical plane, stopping in each rotated position. The doll's eyes reflex should never be performed in the patient with potential cervical spine injury. Presence of the reflex consists of the eyes remaining fixed in gaze during head turning, followed by a return to the resting eye position while the head is still turned. An absent reflex means that the eyes "turn" with the head and never deviate back to midline. It is important to recognize that the doll's eyes reflex can be overridden by higher cortical function in the neurologically intact child. An awake child may consciously not return his or her eyes to midline. The presence of the reflex in the comatose child denotes a functional brainstem that lacks voluntary overriding cortical control. The absence of the reflex (eyes do not return to midline) in a comatose child indicates a loss of both cortical and brainstem control.

The doll's eye reflex should never be elicited in children with suspected spine injury.

Ice water caloric testing occurs after the tympanic membrane is examined, confirmed to be intact, and, if needed, cerumen removed. The patient's head is elevated 30° to orient the horizontal semicircular canal in the vertical plane, and at least 10 mL (more commonly, 30–50 mL) of ice water is irrigated into the ear canal. This causes cooling of the endolymph, increasing its density. The endolymph then migrates downward and, in doing so, mimics a horizontal rotation of the head.

Four traditional responses to cold caloric testing have been described:

1. *Caloric nystagmus* – The examiner observes an initial slow movement of the eyes toward the side of the stimulus, followed by a fast component, the nystagmus which appears as the eye beating away from the side of ice water irrigation. The popular mnemonic "fast COWS" is used to recall the response of *fast* nystagmus occurring after *c*old water instillation *o*pposite the side of stimulation and *w*arm water instillation causing *s*ame sided nystagmus. This response is usually seen in *normal* individuals, psychogenic coma, or in disorders that produce mild alterations in consciousness.
2. *Conjugate deviation* – The examiner observes slow deviation of eyes toward the cold stimulus. Slow conjugate deviation reflects intact brainstem function as well as intact afferent and efferent limbs of the reflex. This is seen during general anesthesia, in supratentorial lesions *without brainstem compression*, and in many metabolic and drug-induced comas. Conjugate deviation suggests cortical compromise but intact brainstem function.
3. *Dysconjugate deviation* – The examiner may observe dysconjugate deviation with early brainstem compression. It should alert the clinician of possible impending herniation. It may also be seen with lesions that preferentially affect the medial longitudinal fasciculus, such as a stroke.
4. *Absent response* – This denotes severe brainstem compromise most often as a result of a supratentorial lesion such as a mass lesion, edema, or cerebellar herniation.

COWS: Cold Opposite Warm Same:
Nystagmus away from stimulation with cold caloric.
Nystagmus toward stimulation with warm caloric.

Gag Reflex

The normal gag reflex is elicited by touching each side of the posterior pharynx with a tongue blade or similar instrument. The full reflex consists of elevation of both sides of the pharyngeal musculature. It should be noted that an absent of a gag reflex occurs in 8–33% of healthy individuals.

The neural pathway of the gag reflex is a simple reflex arc. The afferent limb from the posterior pharynx is carried by the glossopharyngeal nerve (CN IX) to the solitary nucleus in the medulla. There are bilateral projections from each solitary nucleus to each nucleus ambiguous of the vagus nerve (CN X). CN X completes the efferent limb of the reflex back to the pharyngeal muscles bilaterally. Brainstem lesions are a common cause of absence of the gag reflex bilaterally, although a focal lesion of the afferent limb (CN IX) can result in an absent gag. Failure of one side of the pharynx to elevate represents a loss of efferent (CN X) function on the affected side.

24.2.2.2 Integrated Assessment of Brainstem Activity

Other important elements of the brainstem examination are motor responses, respiratory patterns, and hemodynamic changes to internal and external stimuli. Comatose patients often manifest stereotypic motor responses that vary with the location or level of their CNS injury. Although a comatose patient's respiratory pattern can be influenced by therapeutic maneuvers (e.g., sedation, neuromuscular blockade, or mechanical ventilation), specific variations in respiratory pattern can serve to localize the level of injury at the brainstem. Similarly, changes in hemodynamics can also be used to localize brainstem injury, while also being subject to normal physiologic responses or vasoactive agents.

Motor Responses

The progression of stereotypic motor responses occurs when the inhibitory influences of higher CNS centers are lost in a rostral to caudal direction. During this process, the initial sign is usually diffuse hyperreflexia including presence of Babinski signs (extension rather than the normal flexion of the great toe to lateral plantar stimulation) occurring with diffuse cortical or diencephalic injuries.

As cortical injury becomes more pronounced, *decorticate posturing* occurs, initially in response to noxious stimuli. The decorticate posture consists of the combination of adduction of the shoulders and flexion of the upper extremities (elbows, wrists, and fingers) with internal rotation of the hips, extension of the knees and ankles, and plantar flexion of the foot.

Further progression of injury to the lower midbrain or upper pons leads to typical *decerebrate posturing*. The decerebrate posture differs from the decorticate posture with the presence of opisthotonos and the positioning of the upper extremities (internal rotation of the shoulder with extension of elbows and hyperpronation of the wrists). Finally, with progression of injury to the lower pons or medulla, diffuse *flaccid paralysis* ensues.

Respiratory Patterns

The stimulus for a normal rhythmic breathing pattern originates in the brainstem, although higher centers can readily influence respiratory patterns in the non-comatose patient. The dorsal respiratory group, located in the medulla, is responsible for rhythmic inspiration. It receives input from central chemoreceptors located in the brainstem, as well as peripheral chemoreceptors with input from CN IX and X. When the ventral respiratory group is stimulated, active exhalation results; because exhalation is passive in normal individuals,

Table 24.5 Clinical exam findings associated with rostral-caudal progression of central herniation

	Diencephalon	Midbrain	Pons	Medulla
Respiratory pattern	+/– Cheyne-Stokes	Cheyne-Stokes	Hyperventilation (rate and depth)	Apneustic, apnea
			Ataxic	
Pupillary responses	Small; brisk very small changes	Midposition, irregular response to light	Pinpoint	Midposition or dilated; fixed
Oculovestibular reflex	Bilateral tonic deviation toward ice water (intact)		Inconsistently present; may be dysconjugate	Absent
Motor responses	Hyperreflexia, Babinski's sign, +/– decorticate posturing	Decorticate posturing	Decerebrate posturing	Flaccid, none
Cardiovascular changes				Hypertension, bradycardia

this nuclear group is inactive during tidal breathing. There are two additional centers located in the pons: the apneustic center and the pneumotaxic center. The pneumotaxic center is within the upper pons and is responsible for ending the inspiratory period.

Understanding the anatomy of the respiratory centers in the brainstem allows appreciation of how dysfunction at progressively caudal levels leads to serial alterations in the respiratory pattern. Respiratory dysfunction can be traced in a rostral to caudal fashion (Table 24.5). Initially, with generalized cortical dysfunction and impairment at the level of the midbrain, there is increased sensitivity of the lower respiratory centers to chemical stimuli. This leads to the well-described crescendo-decrescendo pattern of breathing familiarly known as *Cheyne-Stokes respiration*. This may be the first sign of transtentorial herniation but may also accompany metabolic disorders or congestive heart failure.

With lesions involving the tegmentum, between the lower midbrain and upper pons, *sustained hyperventilation* occurs. With further damage to the pons, the effects of the pneumotaxic center are lost and *apneustic breathing* (prolonged inspiration followed by expiratory pause) ensues. At this stage, breathing is generally insufficient to maintain adequate gas exchange.

Further progression to involve the apneustic center (lower pontine) and then the medullary respiratory centers leads to *ataxic breathing*, characterized as irregular, ineffective respirations with shallow and deep breaths occurring randomly. Ultimately, further involvement of the medulla leads to *apnea*, and a loss of sensitivity to any chemical stimulus. The above signs are an oversimplification of the function and anatomy of the complex regulatory centers of the brain and should be interpreted with caution. The examiner must keep in mind that changes in the respiratory pattern may also reflect metabolic and neurogenic influences on respiratory centers without corresponding anatomical lesions.

Brainstem-Mediated Hemodynamic Changes

Damage to the medulla often leads to the classically described vital sign changes known as Cushing's triad which is bradycardia, hypertension, and irregular respirations.

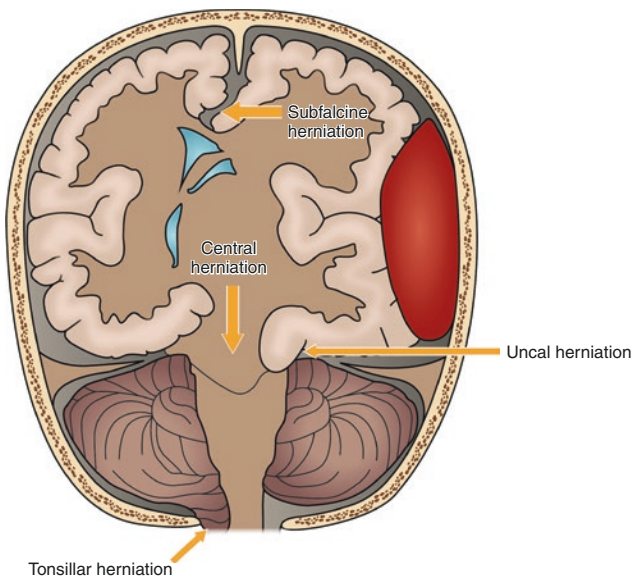
The integrity of the pontomedullary reticular formation and descending pathways is essential in the central regulation of blood pressure and heart rate. However, the regulation of hemodynamics is greatly affected by peripheral influences. As opposed to breathing that depends on CNS input, circulation can exist in the absence of any CNS input. Damage to the medulla often leads to the classically described vital sign changes known as *Cushing's triad* which consists of bradycardia, hypertension, and irregular respirations. Paradoxically, infants and smaller children may manifest Cushing's triad with tachycardia rather than bradycardia. The presence of these specific hemodynamic derangements accompanied by apnea suggests dysfunction at the level of the medulla.

24.2.2.3 Herniation Syndromes

Brainstem dysfunction may herald cerebral herniation and will produce distinct neurologic patterns. The degree of progression is proportional to worsening neurologic outcome.

Brainstem dysfunction may herald cerebral herniation and will produce distinct neurologic patterns (◘ Fig. 24.1). The degree of progression is proportional to worsening neurologic outcome. Irreversible damage may not occur until the development of medullary compression. Early identification of herniation is essential to improving outcome. The most commonly seen herniation syndrome in the pediatric patient is central or rostral-caudal herniation, which occurs when the volume of cranial vault contents increases beyond its compensatory ability. During central herniation, the cerebral cortex is pushed downward, causing first the diencephalon, then the midbrain, and finally, the lower brainstem to become downwardly displaced toward the spinal canal with resulting ischemia. Interestingly, this downward pressure causes most of the injury to the central areas of the brainstem rather than laterally, as occurs in the uncal syndrome. This injury can be severe enough to disrupt the pituitary neuroendocrine function potentially resulting in diabetes insipidus. Uncal herniation is characterized by rapid development of a unilateral fixed and dilated pupil from the compression of CN III.

Understanding the anatomic correlations of pupillary function, eye movements, limb movements, respiratory pattern, and cardiovascular changes allows accurate diagnosis of the degree of herniation; injury to the diencepha-



◘ **Fig. 24.1** Herniation syndromes

lon, midbrain, pons, and medulla all lead to recognizable physical findings. Table 24.5 summarizes these relevant examination findings grouped according to the degree of progression.

24.2.3 Spinal Cord

Spinal cord compression is a neurologic emergency, and prognosis is inversely related to time of symptom onset and treatment.

Spinal cord injury from trauma usually occurs with acceleration/deceleration forces, resulting in severe neuromuscular dysfunction. Demyelinating, space-occupying, and vascular lesions may also lead to spinal cord dysfunction. The hallmarks of spinal cord disease include: level-specific sensory and motor deficits, disturbance of bowel or bladder function, and local spinal pain. Assessment includes: determination of sensation and movement of all extremities, rectal tone, and vital signs. The examination is limited in the patient with altered mental status. Acute spinal cord compression is a neurologic emergency. Prognosis is inversely related to the time between onset of neurologic symptoms and treatment.

The assessment of motor function can also be approached in a rostral to caudal direction. Lack of movement or decreased strength may be caused by the disease of either the corticospinal tract and its neurons (the upper motor neuron, UMN) or the peripheral neuromuscular apparatus, which includes anterior horn cells, ventral motor root, peripheral nerves (lower motor neuron, LMN), the neuromuscular junction, and the muscles.

The thorough neurologic examination distinguishes between upper and lower motor neuron lesions. Several exam findings help delineate the two. Chronic UMN lesions usually produce hypertonic (spastic), hyperreflexive limbs versus acute UMN lesions, which yield flaccid limbs. The Babinski sign is usually present in acute disease. Whereas hemiplegic weakness strongly suggests UMN disease, diseases of the LMN will usually reveal symmetrical, hypotonic, hyporeflexive weakness. Localization of UMN lesions is described in Table 24.6.

Table 24.6 Localization of upper motor neuron lesions

Cerebral hemisphere	Aphasia (dominant hemisphere)
	Cortical sensory loss (graphesthesia, stereognosis, 2 point discrimination)
	Gaze preference
	Unilaterally diminished opticokinetic nystagmus
	Visual field deficit
Internal capsule	Equal paralysis of face, arm, and legs
	Motor loss without sensory symptoms
	Motor loss with dense hemi-sensory deficit
Midbrain	Hemiplegia with contralateral CN III palsy
Pons	Hemiplegia with contralateral CN VI or CN VII nerve palsy
Medulla	Spastic weakness, difficulty swallowing and phonating, incoordination
Spinal cord	Weakness of one leg with contralateral loss of pain and temperature sensation Paraplegia, sensory level, bowel, and bladder dysfunction

Table 24.7 Key neurologic deficits according to cervical nerve root and spinal level

Spinal nerve root	Spinal level	Functional deficit
C5	C4 C5	Respiratory paralysis
		Quadriplegia
		Loss of deltoid
C6	Between C5 and C6	Paralysis of legs, wrists, and hands
		Loss of brachioradialis and biceps
		Loss of forearm pronators/supinators
		Weakened shoulder abduction and elbow flexion
C7	Between C6 and C7	Paralysis of legs, wrists, and hands
		Loss of triceps
		Loss of wrist extensors/flexors
C8	Between C7 and T1	Paralysis of legs and hands
		Loss of finger flexors and extensors
T1	Between T1 and T2	Paralysis of legs
		Loss of finger adductors and abductors

24.2.3.1 Dermatomal Distribution

During the neurologic evaluation, key peripheral nerve and muscle relationships and concomitant spinal reflexes should be assessed. Injury to cervical spinal nerves 3, 4, and 5 which innervate the diaphragm may result in significant or complete respiratory impairment. Injury to thoracic spinal nerves 1 through 12 innervating the chest wall and abdominal muscles may produce respiratory insufficiency, especially if concomitant lung injury is present. Sacral spinal nerves 3, 4, and 5 supply the bladder, bowel, sex organs, anal muscles, and other pelvic muscles.

C 3, 4, and 5 keep the diaphragm alive!

Rectal tone should be assessed in any child with alteration in motor function. Serial physical examinations remain a key element for assessing the extent and severity of injury. Table 24.7 outlines additional signs and symptoms of high spinal lesions. If the patient has no perianal sensation and no voluntary control over his sacral innervated muscles, toe flexors, or rectal sphincter, he is then classified as having a complete lesion. If this condition persists for 24 h, 99% of the patients will have no functional recovery.

24.2.3.2 Spinal Syndromes

Several incomplete spinal syndromes can be identified based on their unique physical exam findings. In a child with *posterior cord syndrome*, caused by injury to the dorsal columns, sense of movement and position (proprioception) and vibratory sensation are impaired.

Conversely, a child with intact proprioception and vibration but loss of pain and temperature sensation may have an *anterior cord syndrome*, with injury primarily affecting the anterior two-thirds of the spinal cord. This type of lesion may be seen in patients experiencing traumatic disc herniation or vascular insufficiency, such as during cardiac or complex spine surgery.

Typically, this will also result in significant motor impairment and sphincteric dysfunction due to the involvement of the ventral horn carrying the lower motor neurons and lateral corticospinal tracts.

Central cord syndrome is caused by injury or edema to the central spinal cord often in the cervical area, for example, in syringomyelia or from athletic injuries in children with congenital stenosis. Central cord syndrome should be considered when a child has greater upper extremity than lower extremity motor deficits, loss of pain and temperature sensation in a cape-like distribution, and possible bowel and bladder dysfunction.

Brown-Sequard syndrome involves hemisection of the spinal cord. Hallmarks of this syndrome include loss of voluntary motor function and proprioception on the ipsilateral side of injury, with loss of pain, temperature, and tactile sense on the contralateral side of injury.

In addition to the described syndromes, spinal shock-associated areflexia in acute injuries and autonomic dysreflexia in chronic injuries must by recognized. The potential for autonomic dysfunction occurs in injuries at or above T6. It may occur with either an internal (e.g., bladder distension) or external (e.g., pain) stimulation of the sympathetic nervous system. This stimulus results in peripheral sympathetic vasoconstriction and hypertension. The subsequent parasympathetic response does not reach below T6 and thus goes uninhibited.

Autonomic dysreflexia is a life-threatening condition where uncontrolled, continuous lower motor neuron reflex arc due to stimulation of sympathetic nervous system results in a parasympathetic response (vagus nerve) sending a stimulus to cause bradycardia. The bradycardia is inadequate to abate the hypertension. Sympathetic response prevails below the level of injury and parasympathetic response prevails above.

Autonomic dysreflexia is a life-threatening condition where uncontrolled, continuous lower motor neuron reflex arc due to stimulation of sympathetic nervous system results in a parasympathetic response (vagus nerve) sending a stimulus to cause bradycardia.

24.2.4 Peripheral Nerve Function

Assessment of the peripheral nervous system (PNS) involves evaluation of motor and sensory function with attention to reflexes and abnormal movements. A full sensory exam requires an alert and cooperative patient. The only sensory responses that can be elicited in patients with depressed mental state are gross responses to pain and the corneal reflex. Painful stimulation that produces a grimace indicates that the sensory message has reached the central nervous system. If painful stimulation produces isolated withdrawal of the limb stimulated, a spinal response is being observed. Note that pain and temperature fibers course along the ventral spinothalamic tract while the dorsal columns carry sensations of position, movement, and vibration. The sensation of light touch has bilateral representation in both dorsal and ventral tracts.

Motor assessment in the awake and cooperative patient evaluates muscle strength, tone, abnormal movements, coordination, gait, and reflexes (◘ Tables 24.8 and 24.9). In the neurologically impaired patient, a focused exam can be followed serially to assess changes in neuromuscular status. Reflexes can be extremely helpful in localization of neurologic dysfunction. Presence of the Babinski reflex indicates acute or chronic injury to the UMN from the cortex to the corticospinal tract in the cord. As previously noted, the presence of a cough and gag reflex reflects glossopharyngeal (CN IX) and vagus (CN X) nerve integrity and the presence of a corneal reflex denotes trigeminal (CN V) and facial (CN VII) nerve integrity.

Babinski reflex is present when dorsiflexion of the great toe occurs in response to stimulation of the lateral plantar aspect of the foot.

Table 24.8 Key elements of the motor examination

Strength	Atrophy
	Fasciculations
	Weakness (scaled 1–5 against gravity)
Tone	Passive
	Active
	Posture
Abnormal movements – spontaneous and induced	Tremor
	Chorea
	Athetosis
	Tics
	Myoclonus
	Dystonia
	Repetitive tonic or clonic (seizures)
Coordination	Finger-to-nose
	Rapid alternating movements
	Heel-to-shin
	Ocular dysmetria
Gait	Spontaneous
	Heel
	Toe
	Tandem

Table 24.9 Numerical scale for muscle strength

Grade 5	Muscle contracts against full resistance
Grade 4	Muscle strength is reduced but muscle can still move against resistance
Grade 3	Muscle strength is further reduced such that a joint can be moved only against gravity with the examiner's resistance fully removed
Grade 2	Muscle can move only if the resistance of gravity is removed
Grade 1	Only a trace or flicker of movement is seen or felt in the muscle
Grade 0	Complete paralysis

24.2.5 Brain Death Determination

In 1987, the American Academy of Pediatrics (AAP) published "Guidelines for Determination of Brain Death in Children" outlining the process of determining brain death in infants and children. These guidelines were updated in a 2011 publication in Critical Care Medicine and endorsed by multiple societies,

including the AAP, Child Neurology Society, and the Society of Critical Care Medicine.

Death by neurologic criteria or brain death is defined by the irreversible loss of whole brain function including the brainstem. The determination of brain death requires three steps: identification of a proximate cause of the child's neurological injury, a thorough and complete neurological examination that confirms the lack of any brain function (brainstem and cortical), and repetition of the evaluation by a different attending physician after a specified period.

The evaluation can only begin after excluding any medical conditions that may confound the clinical assessment. These include severe electrolyte, acid–base, or endocrine disturbances; hypothermia, defined as a core temperature of 35 °C or lower; hypotension; evidence of drug intoxication, poisoning, or neuromuscular blocking agents (see train of four testing below). Medications that may interfere with the respiratory drive should be discontinued and allowed to clear.

Assessment of neurologic function after cardiopulmonary resuscitation or other severe brain injury should be deferred for at least 24 h if there are concerns or inconsistencies in the examination (■ Table 24.10). Ancillary tests are no longer routinely recommended but may be helpful in confirming the diagnosis in cases where clinical examination and/or apnea testing cannot be completed.

The evaluation of brain death can only begin after excluding any medical conditions that may confound the clinical assessment.

Recognizing variability in the adherence to the published guidelines and statutes that may vary by state and even within institutions, the Neurocritical Care Society and others have developed educational resources to reduce potential inconsistencies in the practices among various providers. The use of checklists has proven to be helpful for documentation and serves to promote uniformity and completeness (▶ Box 24.1).

Once the proximate cause of the coma has been determined and is consistent with an irreversible loss of whole brain function and confounding factors are excluded, the examination can proceed. The clinical portion of the *examination* is systematic and begins with determining the presence or absence of

■ Table 24.10 Guidelines for the determination of brain death in children

Clinical
Coma
Absence of motor responses
Absence of pupillary light responses
Absence of corneal reflexes
Absence of caloric responses
Absence of gag reflex
Absence of coughing in response to tracheal suctioning
Absence of sucking and rooting reflexes
Absence of respiratory drive at a $PaCO_2$ that is 60 mm Hg or 20 mm Hg above normal baseline values
Interval between two examinations
Term newborn to 30 days old – 24 h
31 days to 18 years old – 12 h

cortical function. This entails stimulating the patient with noxious *tactile* (nail bed, supraorbital pressure, sternal rub), *auditory* (clap, loud noise) and *visual* (bright light) stimulation, monitoring for any induced or spontaneous brain-initiated response such as seizure, decorticate, or decerebrate posturing. The exam proceeds through the evaluation of brainstem function including cranial nerves, oculocephalic, and oculovestibular testing as detailed previously. If the clinical examination is without evidence of any cortical or brainstem function, the final portion of the exam is the apnea test.

The *apnea test* is performed to confirm the absence of respiratory drive resulting in an elevation of P_aCO_2. Apnea testing must be performed safely and requires documentation of no observed respiratory effort simultaneously with an arterial $P_aCO_2 \geq 60$ mm Hg and a change >20 mm Hg above the baseline P_aCO_2 at the start of the exam. In addition to the requirements excluding confounding medical conditions, the apnea test must be performed in a patient who is eucapneic (P_aCO_2 35–45 mm Hg), not hypoxemic, and is without chronic CO_2 retention. The test should not be performed if there is evidence of residual neuromuscular paralysis or high cervical cord lesions. The first step involves preoxygenation (F_iO_2 100%), raising the P_aO_2 to ensure the patient can tolerate several minutes of hypoxia.

During the testing period, oxygenation can be maintained by providing oxygen flow through a tube inserted through the endotracheal tube or by using a Mapleson circuit. If possible, the patient should be removed from positive pressure via the ventilator to eliminate autocycling confounding the apnea test. Autocycling can occur when the ventilator has no set rate, yet breaths are seen clinically and recorded on the ventilator data screen. The potential reasons for autocycling in brain death depend on the method of ventilator-triggering being utilized: pressure or flow. During pressure-triggered mechanical ventilation, a change in pressure may be sensed (and trigger a pressure supported breath) if an endotracheal tube cuff leak or a large bronchopleural fistula exists. During flow triggering, the ventilator monitors a continuous flow of gas through the ventilator circuit, and a breath is initiated when the return flow is less than the delivered flow. This mode allows patients to initiate breaths more easily, thus decreasing the overall work of breathing. However, this sensitive triggering system can sense cardiogenic oscillations which can trigger mechanical breaths, thus mimicking spontaneous breathing.

During the apnea test, the patient's head, chest, and abdomen should be observed closely throughout the period to detect any evidence of respiratory effort. Reliance on cardiac or other monitors alone should be avoided as transmission of cardiac pulsations can mimic respiratory effort. The patient is observed continuously for a period of at least 5–10 min while maintaining hemodynamic parameters and oxygen saturations. Any evidence of respiratory effort, however insufficient, is not consistent with a diagnosis of brain death, and the test should be immediately terminated. The rate of rise of CO_2 is approximately 3–5 mm Hg/min which can be used to determine how frequently blood gas measurements are obtained. Apnea is confirmed when P_aCO_2 rises ≥60 mm Hg and there is a change of >20 mm Hg from baseline. Testing should be aborted if oxygen saturations falls below 85%, P_aCO_2 fails to rise ≥60 mm Hg or patient becomes hemodynamically unstable. If the apnea test cannot be safely completed, an ancillary study should be performed, but should not be considered a substitute for the neurologic exam.

Ancillary studies are appropriate when a full examination cannot take place, as in the case of extensive trauma precluding oculocephalic and oculovestibular testing, when the apnea test cannot be safely performed, to reduce the observation period between exams and in some social situations in which is it deemed helpful for family members to accept the diagnosis of brain death. Accepted ancillary studies include demonstration of the absence of cerebral blood flow on four vessel angiography, absence of flow on radionucleotide

tracer injection, and presence of electrocerebral silence (ECS) on the EEG. While it is the gold standard used to document absence of flow, angiography is used less often as it requires transfer to the angiography suite, is invasive, and is potentially challenging in the pediatric patient. The EEG is generally available in most, if not all, ICU settings. The diagnosis of ECS is made with a recording of at least 30 min demonstrating no brain-generated waveform activity of >2 μV run at a sensitivity of 2 μV/mm with appropriate filter settings and interpreted by a trained electroencephalographer.

Cerebral blood flow (CBF) studies are performed more often and have a higher sensitivity in younger patients than EEG. The use of a radionucleotide tracer such as Te99 hexamthylpropylene-amine oxime (HMPAO) can qualitatively assess CBF because of its brain-specific uptake. The tracer is injected, and images recorded in the radiology suite under a gamma camera are taken at 30–60 min and then 2 h post injection. Other studies that have been considered as ancillary studies include transcranial doppler (TCD), computerized tomographic angiography (CTA), magnetic resonance angiography (MRA), somatosensory-evoked potentials (SSEPs) have not been validated in the pediatric population given limited data.

Once the history, clinical exam and apnea test determine a complete lack of cortical and brainstem function, an *observation period* is required, and *repeat examination* performed before the patient can be declared brain dead. That period is 24 h in the term infant (>37 weeks) to 1 month of age, and 12 h in infants and children (over 30 days–18 years). The guidelines require that the second examination be performed by a different attending physician who is qualified and competent to perform the examination. The apnea test is again performed in accordance with previous outlined criteria. If the patient has an initial examination that is consistent with brain death, but an apnea test could not safely be performed and an ancillary test that is also consistent with brain death, an observation period with a second examination and second ancillary test is necessary to fulfill the requirements. Neither of the physicians involved in the testing should be members of the transplant team or managing patients who could be potential recipients of donated organs/tissues.

To complete brain death evaluation, a second examination is required before the patient can be declared brain dead.
Interval periods between first and second examination vary based on age. The interval is 24 h in the term infant (>37 weeks) to 1 month of age, and 12 h in infants and children (over 30 days–18 years).

The death of a child is always emotionally challenging, and acceptance of brain death can be confusing to families and difficult for medical professionals to explain. There is an increasing trend to have parents and immediate family members present for the brain death examination. Their presence provides for a greater understanding of the procedure and acceptance in the declaration of death and offers members of the critical care team additional opportunity to support families through the dying process.

Box 24.1 Brain Death Examination Checklist

Patient Age	*Timing of first exam*	*Interval timing between first and second exam*
>37 weeks up to 30 days old	*24 h* after birth, inciting injury, cardiopulmonary arrest	*24 h* OR Interval shortened with ancillary study
31 days old up to 18 years old	*24 h* after inciting injury or cardiopulmonary arrest	*12 h* OR Interval shortened with ancillary study

Brain death determination is performed by two different attending physicians separated by appropriate interval.

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***Prerequisites for brain death examination*:**	**First exam**	**Second exam**
1. *Irreversible etiology of coma*:		
2. *Correction of derangements that may interfere with exam* Core body temperature is ≥35 °C (95° F)		
Systolic blood pressure is ≥2 standard deviations above the age-established norm		
No major metabolic disturbances are present		
All sedatives, analgesics, neuromuscular blockers, or anticonvulsant medications have been discontinued for a period that allows for expected elimination based on individual drug pharmacokinetics		

If all prerequisites are met and the appropriate time interval has passed, pursue brain death examination.

***Physical exam confirming unresponsive coma and loss of all brain stem reflexes*:**		**First exam**	**Second exam**
Flaccid tone, absence of spontaneous /induced movements to noxious stimulation of four limbs and both sides of face, excluding spinal reflexes			
Pupils do not respond to bright light			
Absence of movement of bulbar, facial and oropharyngeal muscles to noxious stimulation			
Absent gag, cough, sucking and rooting reflexes			
Absent corneal reflexes			
Absent oculocephalic reflexes (doll's eyes); exclude if spine injury			
Absent oculovestibular responses (cold calorics); exclude if TMs not intact			
Apnea test: No spontaneous respiratory efforts noted after demonstrating a PaCO2 ≥ 60 mm Hg and an increase of ≥20 mm Hg above baseline.	Baseline $PaCO_2$	*mm Hg*	*mm Hg*
	Test duration	*min*	*min*
	Post-test $PaCO_2$	*mm Hg*	*mm Hg*

Ancillary testing is required if any component of the neurologic examination or apnea testing cannot be completed.

Ancillary testing indications		
Apnea testing cannot be performed to completion Uncertainty regarding results of the neurologic exam Prolonged medication effect present	Either study can be used to reduce interval period between exams If performed, must be completed with both exams	
Ancillary testing	First exam	Second exam
Cerebral Blood Flow (CBF) study is without cerebral perfusion		
Electroencephalogram (EEG) records electrocerebral silence		
Summary of Findings	First exam	Second exam
Prerequisites met		
Coma or Unresponsiveness		
Absence of brainstem reflexes		
Apnea confirmed		
Brain death established by ancillary testing		
First Examiner:	*Date*	*Time*
Second Examiner:	*Date*	*Time*

24.3 Assessment of Cerebral Blood Flow

Functional studies of cerebral blood flow can be assessed by cerebral angiogram, radionuclide imaging, and transcranial Doppler ultrasonography (TCD). Cerebral blood flow studies may be indicated for the identification of vascular occlusion (thrombotic stroke), injury of large arteries (traumatic dissection), and vasculopathy (Moya disease). In the absence of cerebral blood flow, both cerebral angiogram and radionuclide cerebral imaging may be used as ancillary studies in the diagnosis of brain death. TCD is not used in the determination of brain death, as the absence of flow may be technical rather than indicative of loss of brainstem function.

Transcranial Doppler ultrasonography measures blood velocity in the major intracranial vessels as a basis for estimating cerebral blood flow. It is useful in determining the direction of flow and in assessing the presence and risk of vasospasm and stenosis. Transcranial Doppler ultrasonography is utilized as a serial, noninvasive diagnostic, and monitoring tool in children with disorders (e.g., sickle cell disease) that place them at significant risk for stroke.

24.4 Intracranial Pressure Monitoring

Continuous monitoring of intracranial pressure (ICP) is utilized to guide therapeutic interventions for patients with central nervous system dysfunction who are at risk for intracranial hypertension. ICP monitoring is most commonly used in patients with traumatic brain injury. Cumulative evidence suggests better outcomes in children with traumatic brain injury who have ICP-directed therapy.

Although a variety of technologies for monitoring intracranial pressure exist, two systems are commonly utilized:

1. Intraventricular system
2. Intraparenchymal system

Intraventricular catheters are generally inserted into the lateral ventricle using known surface landmarks for guidance. Expertise in this technique is essential for success, especially when the ventricles are effaced or malpositioned because of intracranial pathology. Once in place, the catheter is in direct contact with the CSF-filled ventricular space. The ICP can then be monitored using a pressure transducer and generally reflects the global ICP. Unlike intraparenchymal systems, a ventricular ICP monitor can be recalibrated routinely during its use. Perhaps the greatest advantage of the intraventricular catheter is that cerebrospinal fluid can be withdrawn as a therapeutic maneuver to reduce ICP. Even a small amount of CSF removal may decrease ICP, especially when intracranial compliance is poor and intracranial elastance is high.

An examination of the intracranial pressure–volume relationship reveals a period where compensatory mechanisms allow the addition of intracranial volume (blood, edema, mass) without significant increases in intracranial pressure. Compensatory mechanisms include the redistribution of CSF into the spinal column and venous blood out of the intracranial compartment. Once these mechanisms are exhausted, ICP can markedly increase even with small volume additions to the intracranial compartment. Hence, the availability of an ICP monitor that allows drainage of CSF can be highly therapeutic in a child with elevated ICP. Although historically referred to as a compliance curve, the change in pressure in response to a change in volume describes elastance, which is the reciprocal of compliance (◘ Fig. 24.2).

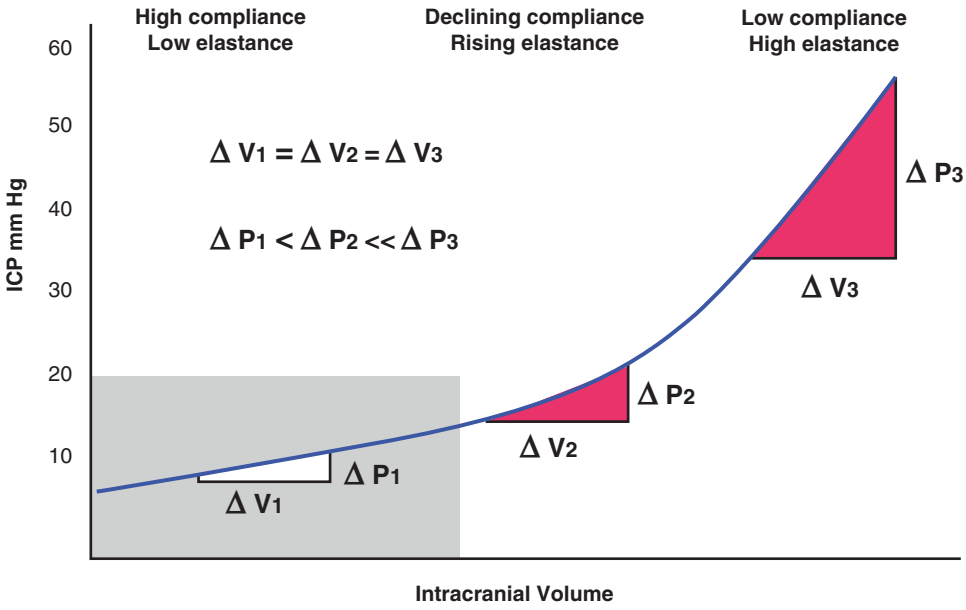


Fig. 24.2 Intracranial pressure–volume relationship. Compensatory mechanisms (*grey area*) allow the addition of intracranial volume (ΔV_1) without significant elevation of intracranial pressure (ΔP_1). Once compensatory mechanisms are overwhelmed, the same change in volume (ΔV_2 ΔV_3) can result in significant elevations of intracranial pressure (ΔP_2, ΔP_3)

When using a ventriculostomy catheter to measure ICP, the CSF drainage port must be temporarily closed, and the stopcock opened toward the pressure transducer to allow accurate ICP measurement.

When using a ventriculostomy catheter to measure ICP, the CSF drainage port must be temporarily closed, and the stopcock opened toward the pressure transducer to allow accurate ICP measurement.

The most common complication of ventriculostomy catheter placement is infection. The reported incidence varies widely but is likely related to total catheter days. In a recent retrospective study comparing infectious complications in ventriculostomy catheters and intraparenchymal monitors, rates of infection were found to be 9.2% and 0.8%, respectively. Data support the use of antibiotic-impregnated ventriculostomy catheters to decrease the risk of infection. Based on the available evidence, the 2016 Neurocritical Care Society consensus statement on neuromonitoring recommended the use of antibiotic-impregnated ventriculostomy catheters, and the Brain Trauma Foundation 4th edition guidelines provided a Level III recommendation for their use to prevent infections. There is insufficient evidence regarding the risks and benefits of prophylactic antibiotic administration with invasive intracranial monitoring.

Other complications of ventriculostomy catheters include hemorrhage, malfunction, obstruction, and malposition.

If an external ventricular drain (EVD) cannot be placed, a catheter can be placed into the brain parenchyma. These catheters consist of a pressure sensing tip using either fiber optic or pneumatic sensors attached to a decoding box. The advantage of these implantable microtransducers are lower infection rates and decreased hemorrhage risk compared to EVDs. However, the pressure that is measured is the tissue pressure surrounding the catheter and may not be as representative of the global ICP as intraventricular catheters. These catheters do not allow for therapeutic withdrawal of CSF. Once inserted they cannot be recalibrated, thus increasing risk of drift and inaccurate readings after sustained use. Table 24.11 provides a comparison of the two systems used to measure ICP.

Intraventricular and intraparenchymal systems enable the clinician to follow the value of the ICP over time and monitor the effect of therapeutic interventions used to treat elevated ICP. Normal ICP in a supine patient is between 7 and 15 mm Hg.

In addition to the value of the ICP, it is important to evaluate the waveform produced during monitoring. Individual waveform analysis and waveform

Table 24.11 Comparison of intraventricular and parenchymal pressure monitoring

	Intraventricular monitor	Parenchymal monitor
Ease of placement	More difficult	Less difficult
Risks of placement	Greater	Less
Pressure measured	Global	Local
CSF drainage	Yes	No
Recalibration possible	Yes	No

trends over time can provide valuable information regarding intracranial compliance and elastance. A noncompliant system will have high elastance; the system will be poorly tolerant of volume increases and will have high recoil upon removal of pressure.

An ICP waveform has three distinct components: percussion wave (P1), tidal wave (P2), and the dicrotic wave (P3). The percussion wave is the first and normally the tallest peak. This initial peak reflects the systolic blood pressure wave that travels through the cerebral arterial system and choroid plexus and ultimately is transmitted to the ventricular fluid. The tidal wave follows and is reflective of rebound pulsations that occur after the percussion wave. The peak of the tidal wave is reliant on reflected waves back from the surrounding intracranial structures and serves as a proxy for the compliance of the intracranial compartment. With decreased intracranial compliance, the tidal wave becomes the dominant peak of the ICP waveform. The final wave (P3) corresponds to the dicrotic notch on the arterial waveform and is thought to reflect venous pulsations (Fig. 24.3).

As intracranial volume increases (e.g., hematoma), compensatory mechanisms to reduce increases in ICP include the redistribution of CSF into the spinal column and venous blood out of the intracranial compartment.

Lundberg initially described ICP waveform abnormalities that occurred over time. Lundberg A waves, known as plateau waves, have a duration of 5–20 min and amplitude of up to 50 mm Hg over the baseline ICP. The plateau pressure may approach the systolic blood pressure. These sustained elevations are often accompanied by neurologic deterioration. When the sustained elevation of ICP resolves, the ICP is reset to a higher baseline level. Lundberg A waves reflect inappropriately high cerebral blood volume due to a disruption in autoregulation and decreased intracranial compliance. Plateau waves can result in a significant decrease in cerebral perfusion pressure (CPP) and may lead to ischemia and worsening of edema. Lundberg B waves are shorter elevations of ICP that last 1–2 min. The amplitude of B waves is typically 10–20 mm Hg above the baseline ICP. They are thought to be related to vasomotor instability but may also be suggestive of worsening of intracranial compliance. B waves are also seen in the setting of abnormal respiratory patterns.

Loss of cerebrovascular reactivity, demonstrated by an ICP that varies directly with the SBP, is an ominous sign.

Intracranial compliance can be assessed dynamically in response to therapeutic interventions. This is most commonly done during the drainage of CSF through an intraventricular catheter. A noncompliant brain will show a greater decline in ICP when a small amount of CSF is drained. Another dynamic approach to assess cerebral hemodynamics is following cerebrovascular pressure reactivity. Cerebrovascular pressure reactivity reflects the capability of cerebral arterioles to react to changes in arterial pressure. With increasing arterial pressure, intact cerebrovascular pressure reactivity will lead to arteriolar vasoconstriction, a reduction of cerebral blood volume and ultimately a decrease in ICP. Conversely, reductions in arterial pressure should lead to dilation of cerebral arterioles to maintain CPP. Cerebrovascular pressure reactivity is essential in maintaining cerebral autoregulation. When cerebrovascular pres-

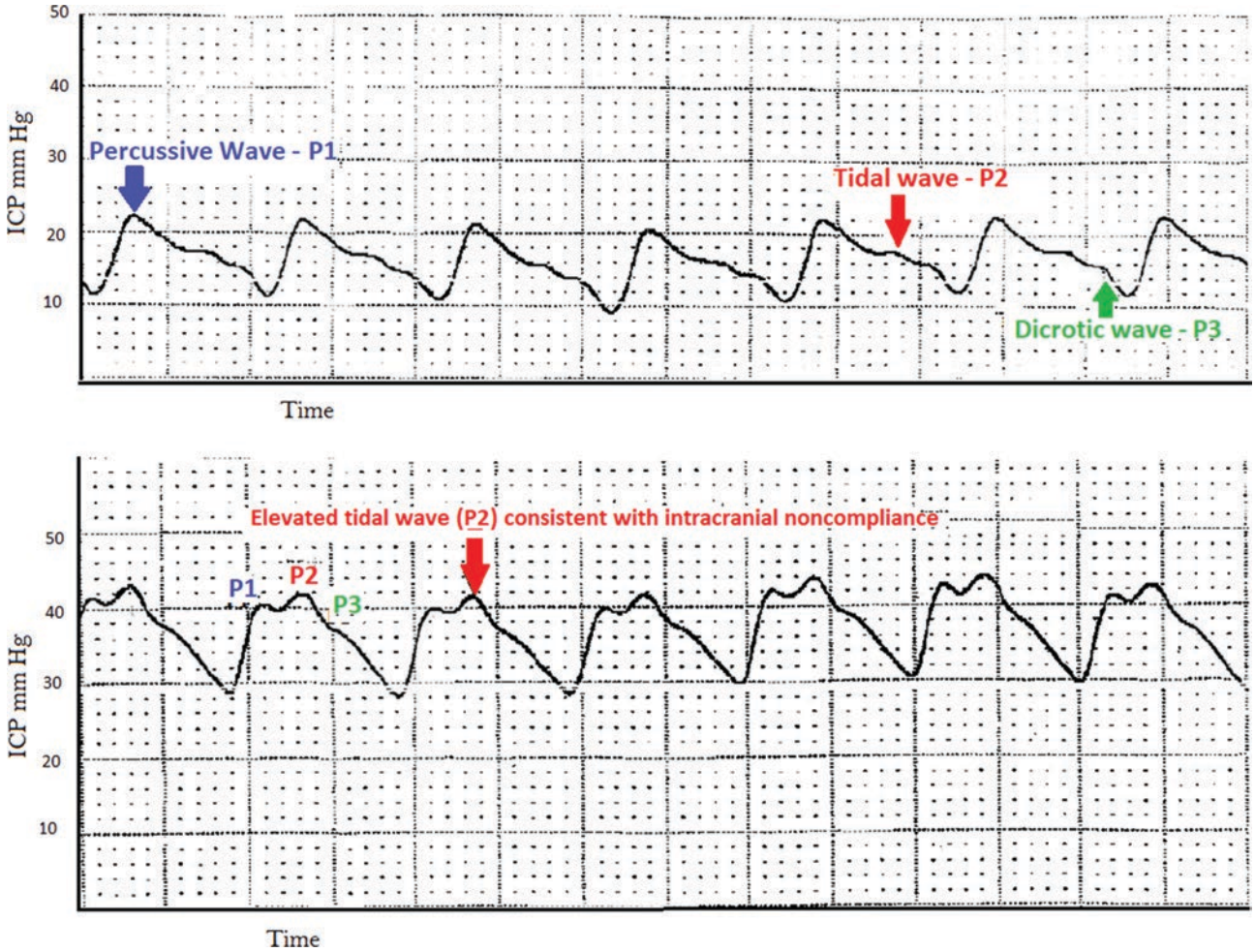


Fig. 24.3 Intracranial pressure waveforms. Top panel shows normal P1, P2, P3 relationship. Bottom panel shows P2 (tidal wave) as the most prominent peak indicating a state of reduced intracranial compliance. (Courtesy F. Maffei)

sure reactivity is impaired, cerebral blood volume and ultimately ICP will increase in response to elevations in systolic blood pressure. Loss of cerebrovascular reactivity has been found to be predictive of poor outcome in traumatic brain injury (TBI). An ICP that varies directly with the systolic pressure is an ominous sign.

24.5 Evaluation of Cerebrospinal Fluid

CSF is produced mainly by the choroid plexus but also by ependymal cells lining the ventricles and spinal cord.

Cerebrospinal fluid (CSF) is produced by the choroid plexus and ultimately resorbed into the venous circulation via the arachnoid granulations. Newborns generally produce about 1 mL/h and have a total CSF volume of about 50 mL. Adults generally produce 20 mL/h and have a total CSF volume of 150 to 200 mL. Normal CSF should be clear and colorless with glucose concentration of one half to one third of the serum glucose, and protein level of 5–40 mg/dL in a child or as high as 65–150 mg/dL in a preterm infant. Presence of white blood cells (WBCs) would normally be an indication of infection, but a few WBCs may be noted in the normal neonate.

A lumbar puncture provides valuable information regarding both the state of the CSF and intracranial pressure transmitted down the spinal column.

Prior to performing a lumbar puncture, the clinician should carefully consider potential contraindications. Lumbar puncture should be performed with full cardiorespiratory monitoring using a small gauge spinal needle; only the appropriate amount of CSF necessary for diagnostic testing should be withdrawn for culture and studies.

Reasons for deferring lumbar puncture have been the subject of much debate. Major contraindications include: the presence of intracranial hypertension, cardiorespiratory instability, or a coagulopathy. A lumbar puncture may acutely decrease spinal pressure and therefore predispose a shift of brain parenchyma down through the foramen magnum. Flexed positioning during the lumbar puncture has the potential to worsen intracranial hypertension. Deep flexion at the neck can obstruct cerebral venous return (increasing cerebral blood volume and ICP), interfere with ventilation, and worsen cardiorespiratory instability by increasing systemic vascular resistance. Bleeding disorders including thrombocytopenia (platelets less than 50 K/uL) or prolonged International Normalized Ratio (INR) (greater than 1.4) may predispose a patient to the development of a spinal epidural hematoma (Table 24.12).

If bacterial meningitis or herpes simplex encephalitis is suspected in a patient who has a contraindication for CSF removal, the lumbar puncture should be deferred. Blood cultures should be obtained, and the child should be treated presumptively with antibiotics and/or antivirals.

A traumatic lumbar puncture occurs when the spinal needle causes bleeding from the venous plexus that encircles the spinal cord as it advances into the subarachnoid space. This introduces RBCs into the CSF sample. CSF protein also increases with a traumatic lumbar puncture: 1 mg/dL for every 1000 RBCs per microL.

Lack of clearing of RBCs suggests malposition or rarely the presence of a hemorrhagic infection (e.g., herpes simplex virus). The presence of RBCs that do not clear and a CSF that demonstrates xanthochromia suggests a subarachnoid hemorrhage (SAH). Xanthochromia is yellow-tinged CSF that appears due to RBC breakdown to bilirubin. Xanthochromia usually begins 2 h after a SAH with 90% of patients displaying the finding by 12 h.

Traditional teaching suggests that for every 500 to 1000 RBCs seen in a traumatic lumbar puncture, 1 WBC is introduced into the CSF. The number of WBCs accounted for by the number of RBCs is subtracted from the number of WBCs observed in the CSF. This would result in a "true WBC" number and would allow interpretability.

Table 24.12 Lumbar puncture indications and contraindications

Indications for lumbar puncture	Contraindications for lumbar puncture
Infection/inflammation (e.g., meningitis and/or encephalitis)	Clinical evidence of increased ICP
Oncologic surveillance	Cardiopulmonary instability
Chemotherapy administration	Coagulopathy, thrombocytopenia (platelets <50,000 uL)
Opening pressure determination (e.g., pseudotumor cerebri)	INR > 1.4
	Overlying skin infection
	Cervical cord lesions

CSF production varies based on age. Newborns generally produce about 1 mL/h and have a total CSF volume of about 50 mL. Adults generally produce 20 mL/h and have a total CSF of 150–200 mL.

Alternatively, a corrected WBC count can be calculated by using the formula:

$$\text{Corrected WBC} = \text{Observed CSF WBC} - \left[\text{CSF RBC} \times \left(\text{Blood WBC} / \text{Blood RBC}\right)\right]$$

Specific CSF proteins can be aid in certain diagnoses. Beta-2 transferrin is formed in the CSF from its serum beta-1 precursor by the action of neuraminidase. It is specific for CSF and its presence has been used as a diagnostic test to detect CSF leakage (e.g., CSF rhinorrhea or otorrhea). Albumino-cytologic dissociation (i.e., raised CSF protein with a normal cell count) can aid the diagnosis of Guillain Barre Syndrome. CSF lactate and procalcitonin have both been found to be elevated in bacterial meningitis.

In addition to laboratory analysis of CSF, opening pressures in a neurologically compromised child may be warranted. Opening pressures will vary based on the patient's age, position, and body habitus. Opening pressure should be obtained in the lateral decubitus position. The mean opening pressure tends to be higher in the flexed position when compared to the extended position, although the difference may not be clinically significant. Normal opening pressure for a newborn is 4–5 cm H_2O and less than 10 cm H_2O in an infant or child (Table 24.13). Opening pressures above 25 cm H_2O in an older child are usually diagnostic of intracranial hypertension.

24.6 Neurophysiologic Monitoring

The purpose of neuromonitoring in the ICU setting is fourfold; to provide diagnosis, guide treatment, aide in prognostication, and to monitor progress and response.

24.6.1 Electroencephalogram

The electroencephalogram (EEG), called by some the "sedimentation rate of the brain," has historically been a mainstay of the evaluation of general cortical function for over three quarters of a century. Standard EEG recordings assess background activity relative to state, symmetry, and evidence of epileptiform activity. In the normal patient, there are well-defined patterns of background rhythms that are seen in specific states of wakefulness and sleep depending on age. Background rhythms should be symmetric bilaterally. Focal cortical insult or seizures originating in one hemisphere may produce obvious asymmetry. The presence of epileptiform activity may help confirm a suspected clinical seizure or prompt the need for continuous EEG monitoring to assess for the presence of nonconvulsive seizures.

EEG remains the only convenient means of continuous, real-time bedside monitoring of brain function supplementing the clinical exam. Recent technological developments have made digital, continuous EEG monitoring widely available, and a necessary mainstay in the PICU setting.

A predictable EEG evolution often follows the progression of cerebral injury. In the intact patient, there will generally be a normal distribution of waveforms appropriate for age. With increasing cortical depression there is typically an increase in slower frequencies, often interpreted as "diffuse encephalopathy," and is nonspecific. Further cortical depression may lead to a burst suppression pattern, with bursts of irregular mixed frequencies spikes followed by relative periods of voltage suppression. Other ominous patterns include alpha or theta coma in which the EEG waveforms are nonreactive to external

Table 24.13 CSF interpretation

	Normal values	*Exceptions*
Glucose	1/2–1/3 of serum glucose	
Protein (mg/dL)	5–40	65–150 in a preterm infant
White blood cells	None	Few may be present in neonates
Pressures (cm H_2O)	<20	4–5 in neonates
		<25 in the severely obese due to increased intra-abdominal pressure
Abnormal CSF values		*Differential diagnoses*
↑ Polymorphonuclear WBCs, ↓ glucose		Bacterial infection
		Parasitic infection
↑ Lymphocytes, ↓ glucose		Mycobacterial infection
		Fungal infection
		Carcinomatous meningitis
		Sarcoidosis
↑ Lymphocytes, normal glucose		Viral infection
		Parainfectious or postinfectious disease
		Parameningeal infection
		Lead intoxication
↑ CSF protein		Infection, fungal, TB
		Venous thrombosis
		Hypertension
		Spinal block
		Guillain-Barré syndrome
Mild CSF pleocytosis		Tumor
		Infarction
		Multiple sclerosis
		Oligoclonal bands (↑ IgG index or ↑ Myelin basic protein)
		Subacute bacterial endocarditis
		CNS vasculitis

or internal stimuli. Finally, marked voltage suppression is seen with severe cortical injury and may progress to the absence of brainwave activity or the electrocerebral silence seen in brain death.

The superficial layer of the cerebral cortex contributes most to the generation of electrical activity detected by the EEG. These areas are selectively sensitive to hypoxia and ischemia. Mild hypoxia may result in subtle decreases in the amplitude of normal fast activity, whereas cerebral infarction or increased ischemia usually results in polymorphic delta (slowing) and more pronounced

attenuation of fast frequencies, including sleep spindles. Additionally, serial EEG can be used to follow neurologic recovery and may demonstrate recovery of brain function from reperfusion earlier than the clinical exam. Focal EEG findings may suggest specific pathological processes, such as lateralized periodic discharges (LPDs) seen in herpes encephalitis.

Status epilepticus (SE) or repetitive seizures without recovery to baseline come in many forms including convulsive (e.g., tonic clonic) and nonconvulsive (e.g., subclinical) or focal with the alteration of awareness. Presentation in some patients may reflect exacerbation of a known clinical condition such as epilepsy or may represent a symptom of an acute illness and therefore a state of electrical irritability within the clinical condition. The exact type of SE that accompanies acute illness may be difficult to differentiate based on observation alone, thus highlighting the importance of continuous EEG (cEEG) monitoring. In many cases the presence of video information is critical to the diagnosis and treatment of the patient. For patients placed in a pharmacologic induced coma, cEEG provides immediate and continuous feedback while monitoring the depth of coma and response to interventions. The ability for cEEG recording to be assessed remotely by the expert physician reader is important for the interpretation and subsequent treatment decisions to be made in real time.

Although cEEG is recorded continuously, rarely is it reviewed continuously. Quantitative EEG (qEEG) algorithms separate raw EEG data into parts and compress several hours of EEG into a single display that allows for rapid analysis by the neurophysiologist and clinicians at the bedside.

Limitations to the use of electrodiagnostic modalities in the PICU include technical (such as interference from existing electronic equipment already in use) and patient specific issues (dressings in place obscuring access for lead placement). When evoked responses are required, these limitations can be magnified.

24.6.2 Evoked Potentials

Somatosensory evoked potentials (SEPs) are generated by the stimulation of afferent peripheral nerve fibers recorded at the somatosensory parietal cortex on the scalp. SEPs can be recorded after either an innate physiologic stimulus (e.g., muscle stretch) or external electrical stimulus. SEPs are most often elicited by the stimulation of the median nerve at the wrist, the common peroneal nerve at the knee, or the posterior tibial nerve at the ankle. The stimulus preferentially excites the largest myelinated fiber in the peripheral nerve. This produces an action potential that travels up the axon to the spinal cord past the cell bodies of the sensory axons in the dorsal root ganglion to the ipsilateral posterior columns of the spinal cord. These signals cross and synapse in the dorsal column nuclei at the cervical medullary junction. The signals then travel in second-order neurons to the ventroposterolateral (VPL) nucleus of the thalamus via the medial lemniscus. In the VPL, a synapse occurs with a third-order neuron that travels to the somatosensory cortex of the parietal lobe. Thus, SEPs provide information concerning the integrity of the pathway from the peripheral nerve, dorsal roots, spinal cord, brainstem, and cerebral cortex (◘ Fig. 24.4).

SEPs can aid in the diagnosis of disorders of peripheral nerve myelination, focal CNS disease, and diffuse CNS disease such as multiple sclerosis and the leukodystrophies. In pediatric critical illness, SEPs are useful in evaluating the comatose child for both diagnostic and prognostic purposes. SEPs are much less influenced by drugs and metabolic derangements than EEG and therefore may be more accurate in prognostication. SEPs have been utilized when the

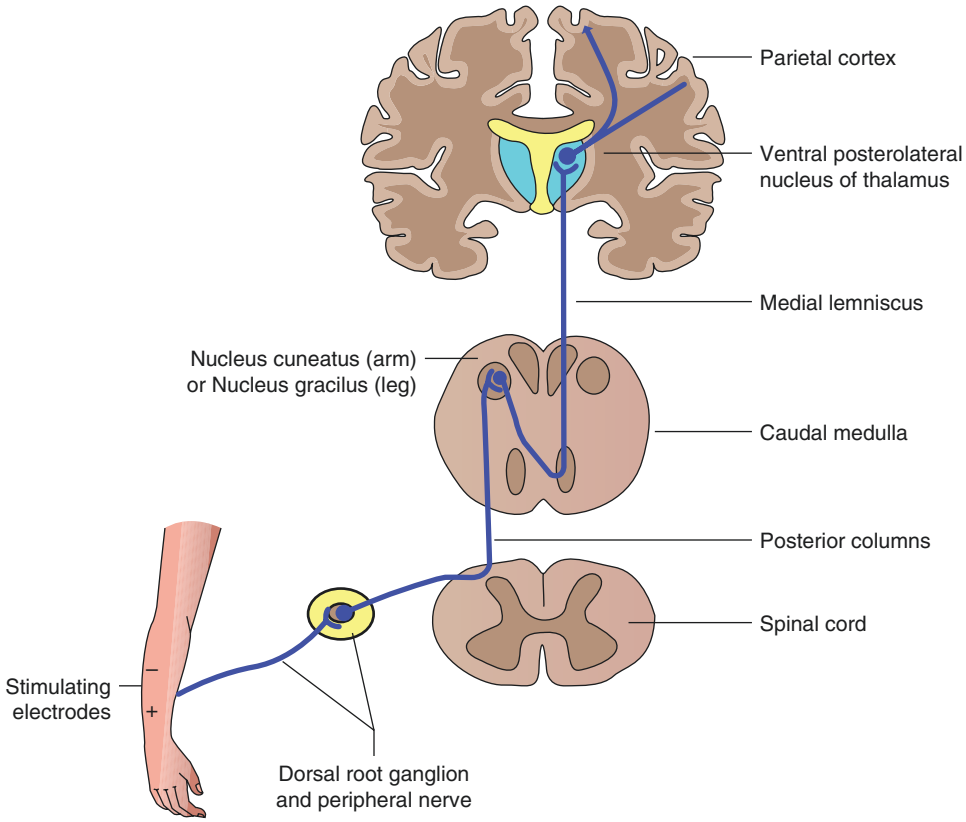


Fig. 24.4 Somatosensory-evoked potential pathways. Electrodes stimulate the peripheral nerve and transmit an action potential through the dorsal roots, spinal cord, medulla, thalamus, and ultimately to the parietal cortex

clinical exam is limited or when confounding factors are present such as extreme hypothermia or prolonged medication effects (e.g., barbiturates, anesthetic agents or muscle relaxants).

In the adult population, a favorable outcome is seen in about 50% of comatose patients with hypoxic ischemic encephalopathy or traumatic brain injury with bilateral intact SEPs. Conversely, the absence of cortical responses bilaterally is associated with a poor prognosis (e.g., severe neurologic deficits or persistent vegetative state). Absence of unilateral cortical SEPs is predictive of hemiparesis but does not preclude favorable outcome. In brain death, peripheral components of SEPs will be preserved, but potentials generated by structures at or above the lower medulla (i.e., cortical responses) are absent.

Brainstem auditory evoked potentials (BAEPs) are used less often in the ICU setting but can be useful in localizing brainstem-specific pathology. Auditory clicks are introduced in each ear producing identifiable waveforms that roughly correspond to their neural anatomic generators as the stimulus passes along the pathway from the peripheral nerve through the brainstem to the medial geniculate body of the thalamus ending in the primary auditory cortex in the temporal lobe.

A somatosensory-evoked potential that demonstrates an absence of cortical responses bilaterally after hypoxic ischemic injury is associated with a poor prognosis (e.g., severe neurologic deficits or persistent vegetative state).

24.6.3 Train of Four

Peripheral nerve stimulation may be utilized in the critical care environment to monitor neuromuscular function especially in a pediatric patient with (prolonged) use of neuromuscular blockade. Neuromuscular blockade has traditionally been monitored by anesthesiologists during surgery by using the number of visible hand twitches after a train-of-four (TOF) peripheral stimulation to the ulnar nerve of the forearm. The clinician must be familiar with

peripheral nerve function and anatomy, as inaccurate placement may cause direct muscle stimulation and a twitch, underestimating the degree of neuromuscular blockade. If four compound muscle action potential (CMAP) responses are identifiable from supramaximal repetitive nerve stimulation (15–60 mAmp) at 2 Hz, the degree of neuromuscular blockade is less than or equal to 75% of complete pharmacologic blockade. TOF testing may not be necessary with serial examinations and neuromuscular blockade breaks. TOF testing must be performed cautiously in the patient who is paralyzed but not adequately sedated due to discomfort.

24.6.4 Multimodality Monitoring

Ideally, continuous neuromonitoring is indicated whenever early detection of a pathologic process may prevent its long-lasting consequences. Crucial clinical scenarios that may require such monitoring are nonconvulsive seizures, increased ICP, and EEG/evoked potential changes reflecting various stages of encephalopathy and/or drug effects. Special consideration in the PICU is the broad range of "norms" from the neonate to young adult brain that preclude the development of universal seizure detection protocols for monitoring. The use of amplitude-integrated EEG (aEEG) in the neonatal ICU has led the way for the development of additional monitoring paradigms in several clinical scenarios such as TBI. Modern digital EEG systems are expanding to include the capacity to present simultaneous polygraphic recordings of pulse oximetry, EKG, respirations, CPP, ICP, tissue oxygenation along with the compressed digital EEG, thus allowing for timely intervention and feedback.

A multimodal neuromonitoring strategy allows clinicians to employ individualized management within the context of protocolized care maximizing therapy and resources. The advantage of incorporating it into the ICU setting is the ability to monitor the unresponsive, comatose, or anesthetized patient and provides quantitative data that can be used to assess efficacy long-term, either serially or comparatively.

24.7 Neuroimaging

The ability to diagnose and treat acute CNS disease has been dramatically improved by advances in imaging techniques. Computerized tomography (CT) provides a rapid assessment of intracranial pathology. Magnetic resonance imaging (MRI) offers further delineation of normal and pathologic structures without radiation exposure (◘ Table 24.14).

The decision to obtain either a CT scan or MRI must be based on the relative risks and benefits of the procedure. For example, CT enables rapid identification of bleeding and skull fractures whereas MRI allows finer assessment of intracranial tumors, posterior fossa pathology, white matter lesions, and ligamentous injury in the cervical spine. Due to its rapid availability, CT is currently the imaging of choice for assessment of acute intracranial pathology particularly in the setting of trauma. MRI duration and inherent difficulties with monitoring while the images are obtained, may limit the use of MRI in some critically ill children.

CT Imaging: CT uses multiple X-ray beams that pass through the brain and differentiate tissue density relative to water; thus highly dense structures, such as an acute bleed, appear white and low-density structures are dark.

MRI Imaging: MRI differentiates tissues by their responses to radiofrequency and identifies small infarcts, infections, inflammatory areas, and demyelinating plaques and better delineates anatomical structures.

Table 24.14 Comparison of neuroimaging modalities

Modality	Advantages	Disadvantages	Indications
Ultrasound	Portable, noninvasive	Limited window, need fontanelle to image brain	Newborn/infant brain, spine Doppler US for arterial/venous flow
X-ray	Cheap, accessible	Limited resolution Radiation	Bony structures, fractures, skull vertebrae
CT	Visualize entire brain, quick	Radiation, limited view of posterior fossa	Acute neurologic assessment, trauma, tumor, calcified lesions, bony structures, skull, vertebrae CT angio or venogram for stroke, examine arteries, veins, sinuses
MRI	Best resolution brain/spine pathology, options for acute neurologic d/o (DWI), vasculature (MRA, MRV), metabolic (MRS), hemorrhage (SWI)	Scan time >20–30 min, may require sedation, contraindications: pacemaker, aneurysm, surgical clips, braces Gadolinium retention +/– years	Brain, spine assessment T1 anatomy T2 pathology Gd+ infection, inflammation, tumor

24.7.1 Computed Tomography

Computed tomography utilizes X-ray beams directed at multiple angles through the body to produce a computer-generated image. The image is made up of thousands of tiny squares or pixels. The pixels have varied X-ray absorbencies based on the density of the tissue. The absorbencies of the X-rays are measured in Hounsfield units (HU). The denser the tissue is the higher the HU, ranging from negative 1000 HU (air), 0 HU (water) to positive 1000 HU (bone) (Fig. 24.5). The obvious disadvantage of CT is exposure to radiation. Advantages to a CT scan include rapid (minutes) assessment of acute neurologic pathology and better detection of traumatic blood and boney structures.

A rapid assessment of the CT image can be accomplished using a systematic approach (Table 24.15). The presence of pathologic masses should be quickly ascertained. The cortical grey and white matter should be examined. In the normal cortex, the differentiation between gray and white matter is quite clear, sulci and gyri are well delineated, and the lateral ventricles are normal and symmetric in size. Brain edema makes the differentiation less clear. Progressive edema may cause ventricular effacement and distortion of the cisterns. Figure 24.6 demonstrates the normal appearance of the quadrigeminal cistern and the suprasellar cistern and defines their surrounding structures.

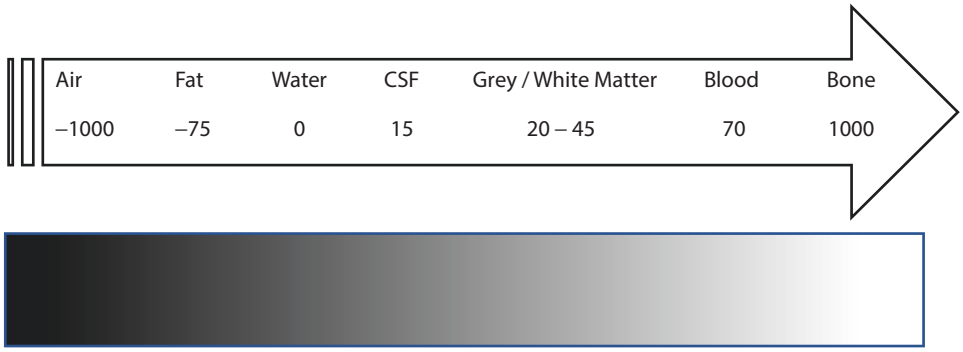


Fig. 24.5 Hounsfield unit scale

Table 24.15 Systematic approach to the evaluation of CT scan

Pathology	Action
Mass	Assess for obvious volume occupying lesion (blood, tumor, foreign body)
Brain parenchyma	Assess gray-white differentiation and presence of edema
	Assess architecture (sulci and gyri) and organization
	Assess for asymmetry or shift
Ventricles	Assess ventricles (size, position, presence of blood)
	Assess suprasellar and quadrigeminal cisterns
Bone	Assess skull and facial bones for fracture

As intracranial pressure increases, the cerebral cortex is pushed downward and impinges on the quadrigeminal cistern posteriorly and the suprasellar cistern anteriorly. These spaces may become completely obliterated during rostral-caudal herniation (Fig. 24.7). Lastly, the skull and facial bones should be assessed for fracture.

24.7.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) uses hydrogen's elemental properties of magnetism and spin to ultimately generate an image. The hydrogen nucleus has one proton that is charged and spins along its axis. When placed in a magnetic field, hydrogen protons align and rotate around the axis of the field, like spinning tops on a table. The proton spins faster as the strength of the magnetic field increases. Once the protons are spinning in a stable manner in the magnetic field, the system is "perturbed" by a pulsed radio wave. If a radiofrequency (RF) is pulsed at the same frequency of the spinning nuclei, resonance occurs and causes the protons to flip, becoming aligned in the opposite direction of the field. When the pulse is turned off, the nuclei get rid of the energy they absorbed. The protons tend to return to their "preperturbed" equilibrium state, such that longitudinal magnetization is at its maximum value and

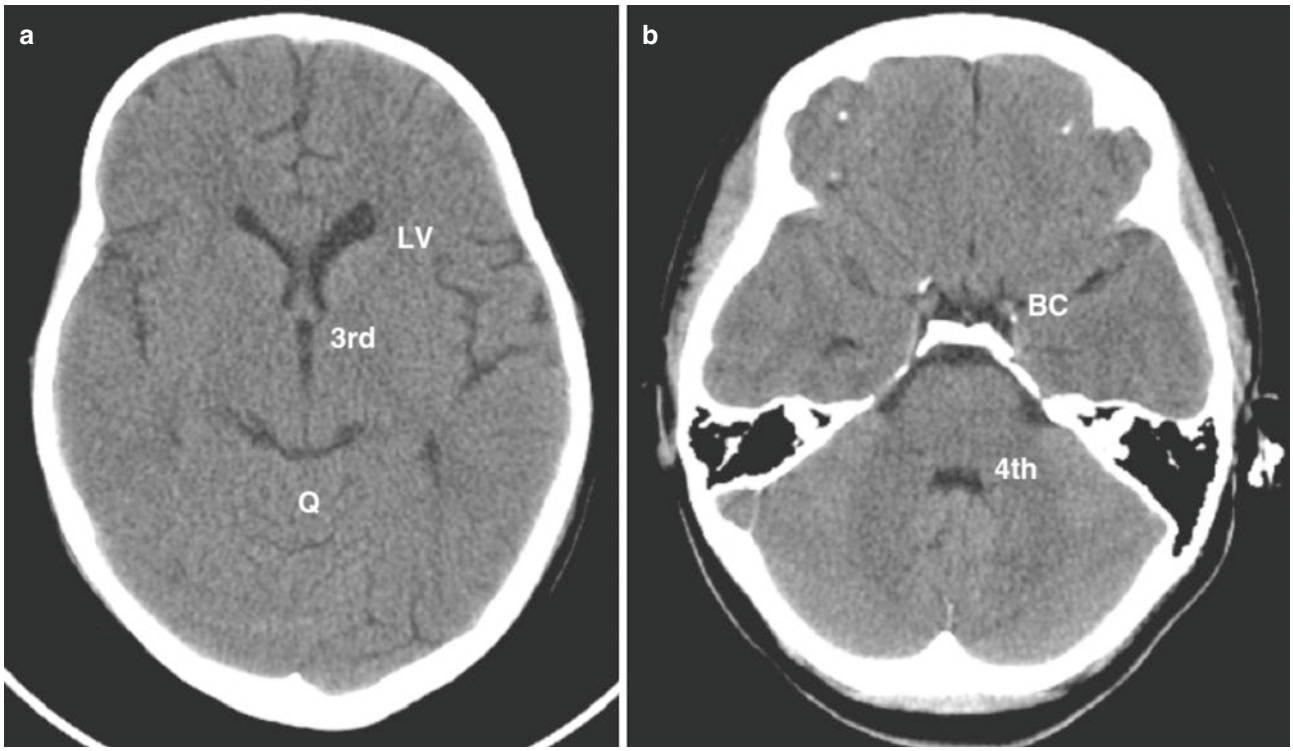


Fig. 24.6 Normal appearance of the **a** quadrigeminal cistern, 3rd ventricle, lateral ventricles and **b** 4th ventricle with basilar cisterns and surrounding structures

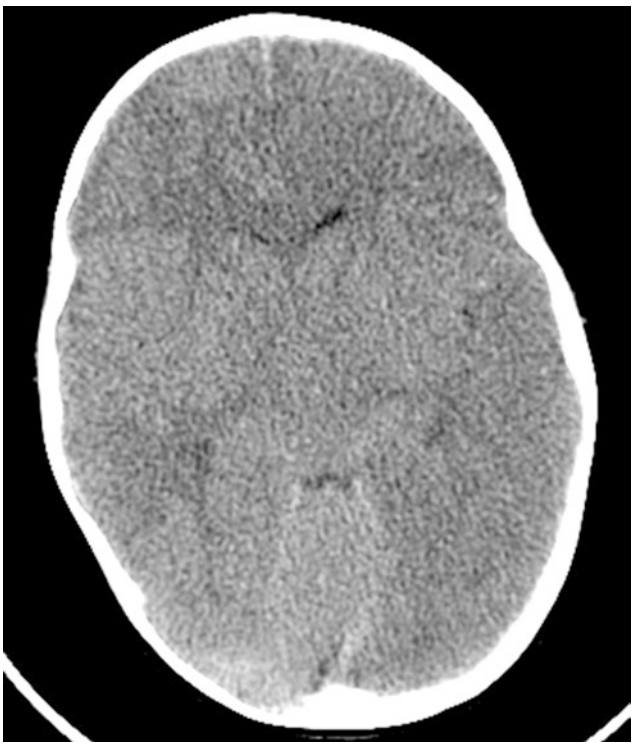


Fig. 24.7 Diffuse edema and herniation causing obliteration of 3rd ventricle, quadrigeminal cistern, and near obliteration of lateral ventricles

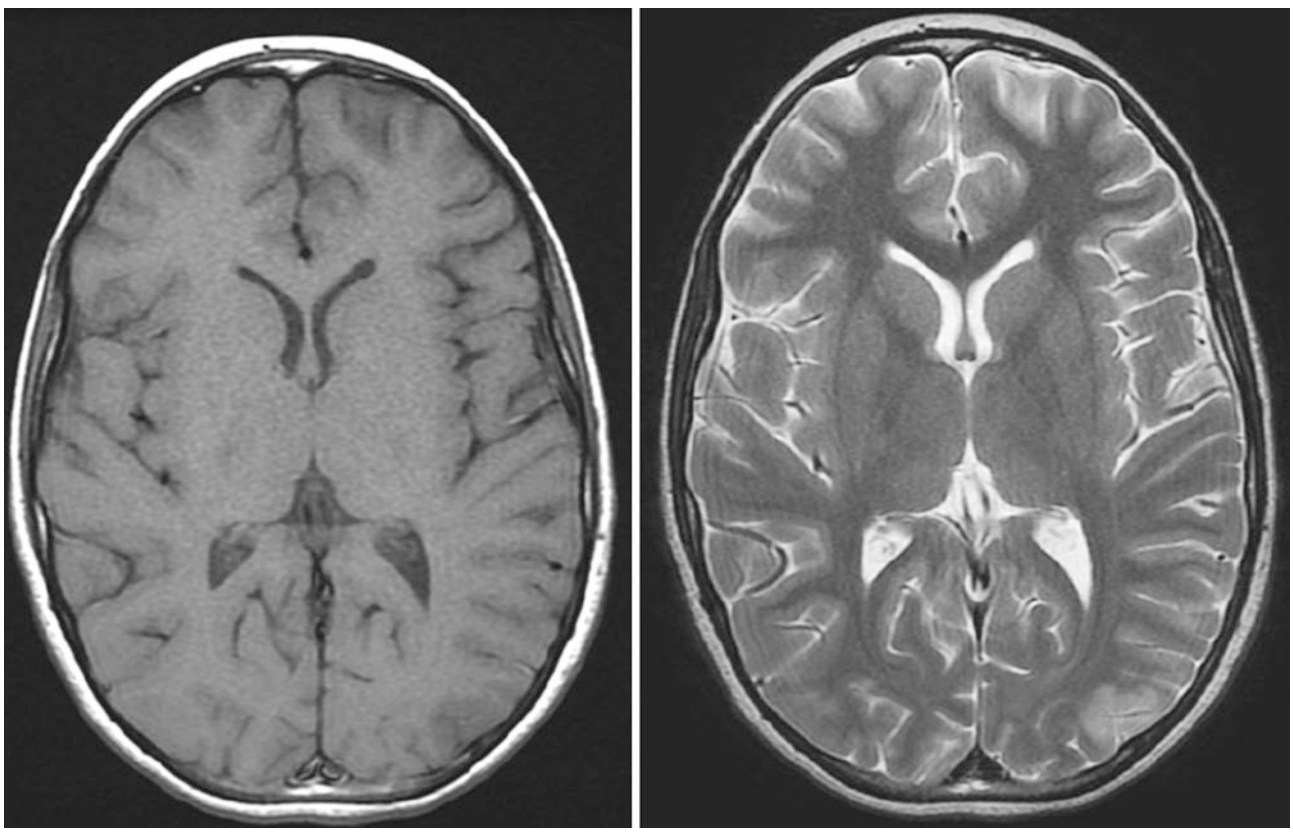
oriented in the direction of the magnetic field and no transverse magnetization exists.

T1 relaxation refers to the characteristic time constant required for the longitudinal magnetization to return to equilibrium. T2 relaxation refers to the time constant required for transverse magnetization of the protons to decay to zero.

The primary determinants of signal intensity and contrast are the character of the pulse delivered, the density of the protons in the tissue and the relaxation times. The times required for protons to return to maximal longitudinal magnetization (T1 relaxation time) and to zero transverse magnetization (T2 relaxation time) vary based on individual tissue characteristics, delivery of the pulse, and the point at which the image is generated. The amount of time that exists between successive pulse sequences is referred to as the repetition time.

Short repetition times are used to produce T1 contrast, while long repetition times generate T2 contrast. Because tissues (blood, fat, bone) have different relaxation times, these differences can be used to create contrast between tissue types when generating an image. By varying the number, timing, and strength of the delivered RF pulse (pulse sequencing), further image manipulation and tissue contrasting can occur.

CSF appears distinctly different on T1-weighted versus T2-weighted images. On T1 images, the CSF will appear dark whereas CSF is bright on T2 (◘ Fig. 24.8). Pathology will appear different on MRI based on the selected relaxation times. Generally, T2 images are more sensitive for intracranial pathology than T1. Infarction and tumors appear bright on T2 images and dark on T1 (◘ Table 24.16).



◘ **Fig. 24.8** Comparison of T1 versus T2 relaxation time. Image on left is T1 image demonstrating dark CSF as opposed to image on right demonstrating bright CSF

Table 24.16 Anatomy and pathology appearance based on neuroimaging

Anatomy/pathology	CT	MRI T1	MRI T2
Bone	Bright	Dark	Dark
CSF or water	Dark	Dark	Bright
Air	Dark	Dark	Dark
Fat	Dark	Bright	Bright
Blood[a]	Bright	Bright to dark	Bright to dark
Infarction	Dark	Dark	Bright
Solid mass	Dark[b]	Dark	Bright

Notations:
[a]Blood on MRI image may be dark if bleeding is hyperacute or chronic[b]Calcifications or hemorrhage within a solid will appear bright on CT

Table 24.17 Blood appearance on MRI based on timing and relaxation time

MRI appearance of blood based on timing and imaging sequence	T1	T2
Hyperacute bleeding < 24 h	Isodense	Bright
Acute bleeding 1–2 days	Isodense – Dark	Dark
Early subacute 2–7 days	Bright	Dark
Late subacute 3–14 days	Bright	Bright
Chronic > 14–28 days	Dark	Dark

Hemorrhage on MRI has highly variable imaging characteristics that depend on the age of the blood, the type of hemoglobin (e.g., oxyhemoglobin, deoxyhemoglobin, or methemoglobin), and the presence of breakdown products (e.g., ferritin, hemosiderin). Other factors that affect MRI appearance are vascular integrity and the specifics of the MRI sequence (e.g., relaxation times).

These differences are summarized in Table 24.17.

Fluid attenuation inversion recovery (FLAIR) is based on T2-weighted imaging in which fluid (e.g. CSF) is suppressed or nulled to enhance the signal effect of lesions in periventricular or subarachnoid regions.

Diffusion-weighted imaging (DWI) is a technique that utilizes the Brownian movement of water molecules to identify acute and subacute edema. DWI senses a restriction of the normal Brownian movement of extracellular water molecules. Pathologic restriction of water movement may be caused by failure of cell membrane pumps responsible for maintaining ionic gradients. This failure can cause cytotoxic edema. Cellular swelling further restricts extracellular water molecule movement by crowding out extracellular pathways. Lastly, cell death leads to the release of cellular components (e.g., membranes, mitochondria, endoplasmic reticulum, proteins) which increase extracellular viscosity, further impeding water movement. The more restricted the movement of water, the greater the signal intensity and the brighter the tissue will appear on DWI. The less restricted the movement of water, the less the signal intensity and the darker the appearance on DWI.

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The less restricted the movement of water, the less the signal intensity and the darker the appearance on DWI. The more restricted the movement of water, the greater the signal intensity and the brighter the tissue will appear on DWI.

CSF contains the least restricted water movement in the brain and will be dark on DWI. Ischemic areas will have restriction of water movement and will appear bright on DWI. Ischemic changes can be detected using DWI much earlier than on T2 and FLAIR imaging, thus making DWI an extremely valuable tool for the early detection of edema resulting from diffuse axonal injury (DAI) or acute ischemic stroke (Fig. 24.9). Restricted diffusion typically occurs within 30–120 min after a cerebral injury, returning to normal by 10–14 days.

Diffusion tensor imaging (DTI) is an extension of DWI that has the potential for improved early diagnosis of diffuse axonal injury (DAI) and post-concussion syndrome (PCS). DTI measures the diffusion of water molecules across the white matter tracts and determines the structural integrity of those tracts by looking at both direction and rate of diffusion. The rate of diffusion is measured by the apparent diffusion coefficient (Fig. 24.10) whereas the direction is measured by the fractional anisotropy. Water molecules are known to move more quickly when parallel rather than perpendicular to nerve fibers. This characteristic is proportional to the thickness of the myelin around the axons. In TBI, changes in diffusion or anisotropia are used as markers for structural alterations that correlate with damage to white matter fibers or neuronal cell bodies. These techniques have been especially useful in assessing the integrity of the corpus callosum in TBI and may be correlated with neurocognitive functions, post-concussive symptoms, and quality of life. Thus, although

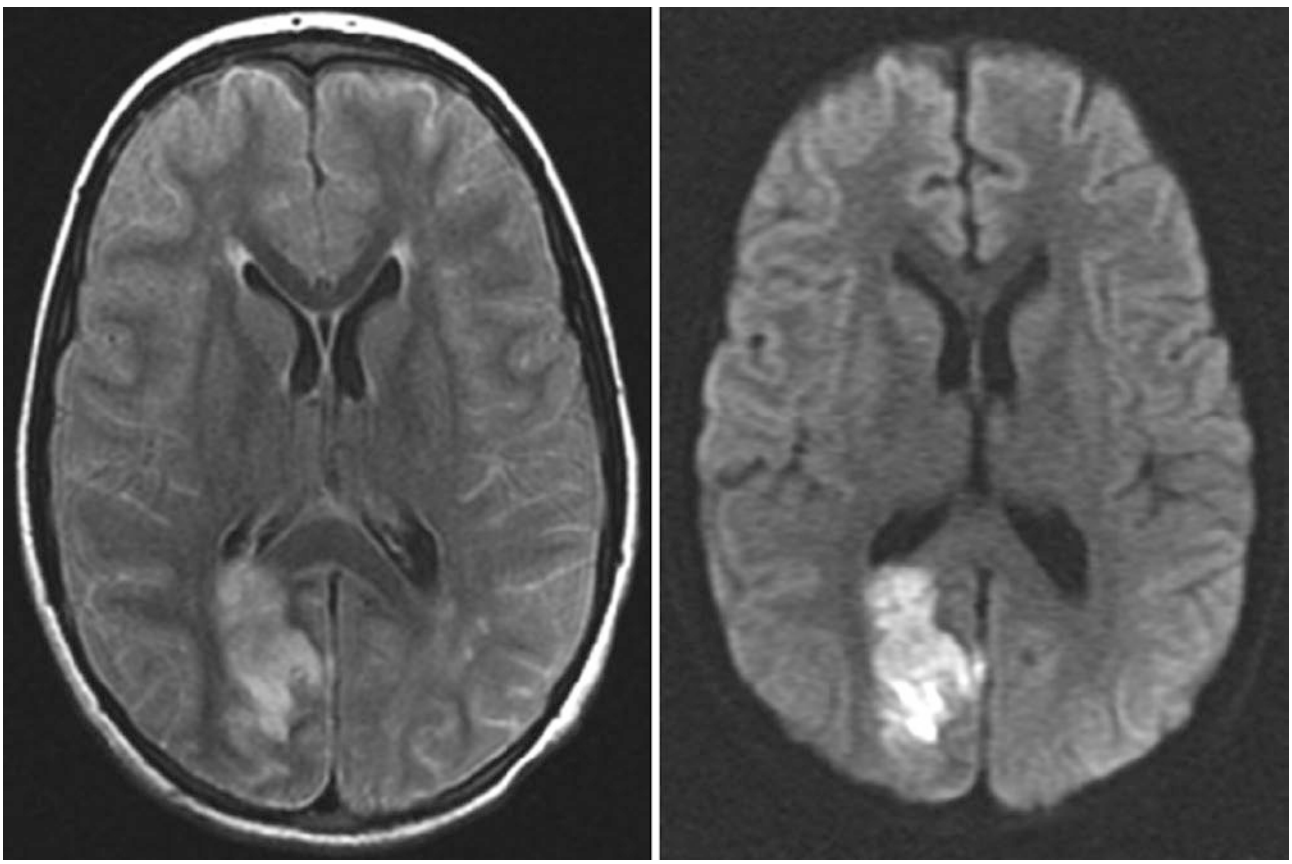

Fig. 24.9 Comparison of acute infarction on MRI FLAIR (*left*) versus MRI DWI (*right*). Dark CSF on FLAIR allows better visualization of periventricular brain matter. The presence of a hyperintense signal on the DWI confirms the acute nature of the infarction

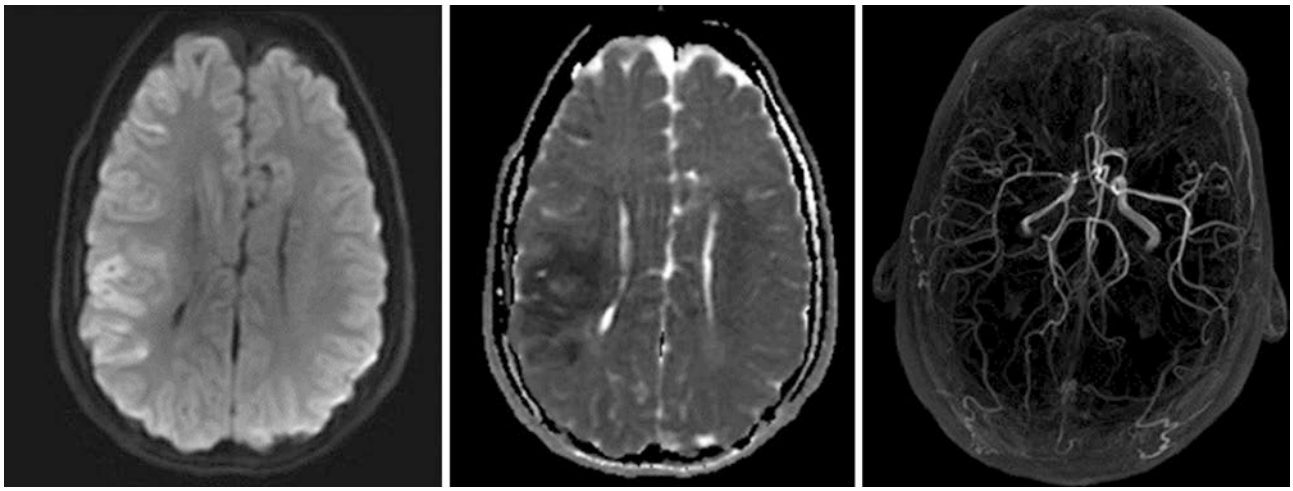

Fig. 24.10 MRI of a 13 yo female with a right middle cerebral artery territory infarction. Diffusion-weighted imaging (*left*) and apparent diffusion coefficient (*middle*) show cortical and subcortical restricted diffusion in the right frontal and parietal lobes. Maximal intensity projection of 3D time-of-flight MR angiography (*right*) reveals diffuse narrowing of the right internal carotid artery and MCA, consistent with vasculitis

Table 24.18 Comparison of MRI modalities

MRI modality	Indications
T1	Good for defining anatomy
T2	FLAIR, demonstrates many types of pathology
Diffusion weighted imaging (DWI) Diffusion tensor imaging (DTI)	Acute pathology, stroke, HIE, infarction
Susceptibility weighted imaging (SWI)	Hemorrhage, mineralization
MRA/MRV	Blood flow, thrombotic disease, vascular anomalies
MRS	Metabolic derangements in tissue, HIE, tumor, metabolic disorders (MELAS), metabolites in given volume of brain tissue (N acetyl aspartate NAA peak in TBI)
fMRI	Uses blood-oxygen level dependent (BOLD) technique to measure cerebral activity in response to stimulation. Newer strategies are looking at "resting state" networks

not yet used clinically, DTI may be better at assessing functional disturbances caused by mild TBI not characterized by CT or conventional MRI. A summary of the MRI modalities is outlined in Table 24.18.

The addition of a contrast agent during MRI can enhance arterial or venous pathology. MRI intravenous contrast agents are termed paramagnetic agents and gadolinium is the most commonly used agent. Unlike conventional contrast agents used in CT, the gadolinium is not directly visualized. Instead, it is the effect of gadolinium on protons in the blood that changes the MRI signal intensity of the blood and allows visualization.

In comparison to CT, obtaining an MRI takes substantially longer and requires special medical MRI-safe equipment that do not contain ferromagnetic material. In addition, MRI requires cooperation by the non-comatose patient. There is concern among clinicians about the effects of anesthesia and sedation on cognition and the developing brain, particularly in younger patients. Many institutions have implemented rapid (e.g., Fast Brain) MRI protocols that eliminate the need for sedation and focus on using limited sequences to address specific areas of concern. This is especially important in patients who require repeated studies, such as those with known intracranial pathology or presence of a ventriculoperitoneal shunt.

Advantages of an MRI include no radiation exposure, improved definition of lesions and their anatomical relationships, demonstration of blood flow and cerebrospinal fluid flow, and evaluation of tumors in the posterior fossa normally obstructed by bone artifact in CT.

24.8 Biomarkers

Neural-specific biomarkers may be useful as indicators of brain injury from ischemia, trauma, inflammation, or other pathologic processes. In settings where the blood brain barrier is breached, biomarkers can be measured in the CSF, serum, and urine. Developing peripheral serum markers for diagnosis and prognosis in brain injury would be advantageous as a relatively non-invasive way of recognizing and serially following injury. However, the utility of biomarkers has not been fully established in children, although several have been investigated recently, including S100B (calcium binding astroglial protein), neuron-specific enolase (NSE) myelin basic protein (MBP), and glial fibrillary acid protein (GFAP).

S100B and GFAP are elevated in settings of acute astroglial injury, and degree of elevation has been associated with the severity of TBI as demonstrated by GCS score and imaging correlates. Some studies have suggested that peripheral levels of S100B and GFAP may successfully delineate mild and severe TBI, potentially determining which patients require CT imaging.

NSE is a biomarker of acute neuronal injury; however, its specificity is limited by its natural presence in erythrocytes and elevation during hemolysis. It has not been well studied in mild TBI, but there are studies of severe TBI that noted the magnitude of peripheral and CSF elevation associated with higher mortality and more severe GCS in both adults and children.

Other spectrin breakdown products, like UCH-L1, have been detected in the serum of patients with mild and moderate TBI within 1 hour of injury. Serum levels have been shown to differentiate concussion patients from uninjured and non-head-injured trauma control patients. UCH-L1 has been shown to correlate with Glasgow Outcome Score (GOS) more strongly than those with either NSE or S100B. With further study, neural specific biomarkers may provide a prognostic, diagnostic, and monitoring adjunct in neurointensive care.

24.9 Conclusion

Despite dramatic advances in imaging techniques and improvements in physiologic monitoring systems, the serial physical examination remains the most critical component of ongoing neurologic assessment. A functional understanding of neuroanatomy and physiology greatly enhances the intensivist's ability to define neurologic deficit and, in turn, execute the most appropriate treatment modalities.

Review Questions

1. While watching a baseball game, a 7-year-old girl is struck in the head with a foul ball. EMS arrives to find her mumbling incomprehensibly and a deep noxious stimulus causes her to withdraw and open her eyes. What is her GCS score?
   A. 10
   B. 8
   C. 6
   D. 7
   E. 9

2. A 15-year-old attending football camp sustained an injury following a tackle that resulted in decreased strength in his upper extremities and urinary retention; lower extremity motor function was noted to be intact. What additional findings are likely to be discovered on his physical exam?
   A. Loss of pain, temperature, and tactile sense on the contralateral side of injury
   B. Loss of pain and temperature sensation in a cape-like distribution
   C. Loss of proprioception below the level of injury
   D. Loss of proprioception on the ipsilateral side of injury
   E. Loss of pain and temperature sensation on the ipsilateral side of injury

3. A 2-week-old infant developed devastating neurologic injury following abusive head trauma. A pediatric intensivist has examined the patient and performed an apnea test and the patient is without any brainstem or cortical function. Which of the following statements is true?
   A. This infant is considered brain dead.
   B. This infant would be considered brain dead if a separate physician performed a complete neurologic exam and apnea test 12 h following the first and confirmed lack of brainstem and cortical function.
   C. This infant would be considered brain dead following a radionuclide cerebral blood flow study that confirmed no perfusion.
   D. This infant would be considered brain dead if a separate physician performed a complete neurologic exam and apnea test 24 h following the first and confirmed lack of brainstem and cortical function.
   E. This infant would be considered brain dead if the same pediatric intensivist performs another complete neurologic exam and apnea test 12 h following the first and again confirmed lack of brainstem and cortical function.

4. A 10-year-old boy with a history of Lennox Gastaut syndrome who had been stable on a combination of valproic acid, levetiracetam, and clonazepam is found in bed with eyes open but unresponsive to his name being called. He has fine twitching movements of his mouth and eyes. What is the most likely diagnosis and what should be the next step in treatment?
   A. Drug toxicity from his combination of anticonvulsants. Obtain levels and hold further dosing.
   B. Post-ictal state. Monitor the patient clinically, continue present medications.
   C. Normal sleep state. Allow the patient to sleep and awaken on his own.
   D. Nonconvulsive status epilepticus. Obtain levels, treat with benzodiazepine, continuous EEG monitoring.
   E. Undiagnosed head injury. Requires urgent imaging and neurosurgical evaluation.

5. A 6-year-old with a history of congenital heart disease repair presents with sudden slurred speech, right gaze preference, and tripping with decreased right grip strength and facial droop. What is the most appropriate diagnostic study?
   A. Head CT with and without contrast
   B. EEG to evaluate for new onset seizure
   C. MRI with DWI sequences
   D. LP to rule out HSV encephalitis
   E. Toxicology screen for heavy metals

6. A 3-year-old male fell out a second-story window and was unconscious at the scene. He arrives intubated with a cervical collar in place. With deep noxious stimuli, he opens eyes and has abnormal flexion of bilateral upper extremities toward his body. This child's GCS upon arrival to the ED is?
   A. 4 T
   B. 5 T
   C. 6 T
   D. 7 T
   E. 8 T

7. While performing a cranial nerve exam, it is noted that the patient does not have a cough or gag. Which cranial nerve(s) are dysfunctional?
   A. VII, X
   B. VIII, IX
   C. IX, X
   D. XI, XII
   E. XII

8. During a neurologic examination, the examiner tests for the doll's eye reflex and observes that the eyes "turn" with the head and never deviate back to midline. Which of the following statements is true?
   A. The absence of the reflex in a comatose child indicates a functional brainstem that lacks overriding cortical control.
   B. The absence of the reflex in a comatose child indicates a loss of both brainstem and cortical control.
   C. The presence of doll's eye reflex indicates a nonfunctional brainstem and cortex.
   D. The reflex can be absent in the neurologically intact child because of involuntary brainstem suppression of the reflex.
   E. The testing of the reflex can be safely performed in all comatose children.

9. A 16-year-old male sustains a spinal cord injury to C7–T1 (C8 nerve root) during a football game. Which physical exam finding is consistent with the injury?
   A. Loss of deltoid function
   B. Loss of finger flexion
   C. Loss of forearm pronation
   D. Loss of shoulder abduction
   E. Loss of wrist flexion

Answers

1. B
2. B
3. D
4. D

5. C
6. C
7. C
8. B
9. B

Suggested Readings

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Cerebral Resuscitation and Traumatic and Hypoxic-Ischemic Brain Injury

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Contents

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Learning Objectives

- Define the difference between primary and secondary brain injury.
- Describe the cascade of events that occurs with global cerebral hypoxia-ischemia and reperfusion.
- Identify possible strategies for attenuating the poor outcomes associated with global cerebral hypoxia-ischemia and traumatic brain injury.
- Describe the modalities currently available for clinical monitoring in brain-injured patients and outline indications for the use of:
  - Intracranial pressure monitoring
  - Brain tissue oxygen monitoring
  - Radiographic studies
  - Electroencephalography
- Review clinical trials in global cerebral hypoxia-ischemia and traumatic brain injury.
- Understand outcomes associated with global cerebral hypoxia-ischemia and traumatic brain injury.
- Describe the initial evaluation and evidence-based ICU management for a patient with hypoxic-ischemic and traumatic brain injury.

25.1 Introduction

The need for improved cerebral resuscitation was born out of progress – advancements in cardiopulmonary resuscitation (CPR), intensive care, and rehabilitation have decreased mortality associated with brain injury in infants and children, but increased the number living with disability. Indeed morbidity, and mortality for that matter, remains unacceptably high. To date, cerebral resuscitation after global hypoxic-ischemic injury due to cardiac arrest and traumatic brain injury (TBI) remains largely supportive, although many promising therapies are being explored at the bench and some at the bedside. Our challenge is to move innovative and effective therapies to the bedside to prevent and/or attenuate irreversible neurological injury and to assist children and families in recovery to attain improved outcomes and quality of life. In the interim, optimizing patient care management in the prehospital setting, emergency department, pediatric intensive care unit (PICU), and rehabilitation facilities is our greatest opportunity for improving outcome in these pediatric patients.

25.2 Mechanisms of Brain Injury

Acute brain injury, such as that seen after ischemia and trauma, involves both primary and secondary injury (Fig. 25.1). After cerebral ischemia, primary injury relates to profound and irreversible ischemia to the point of cellular membrane failure, swelling, and lysis prior to reperfusion. Morphologically, this form of cell death is referred to as necrosis. After TBI, primary injury refers to direct mechanical disruption of brain parenchyma. Since this also includes disruption of the cerebrovasculature, ischemia can also contribute to primary injury after TBI.

Secondary brain injury represents the evolution of tissue damage after the primary insult. This is of obvious importance given that secondary injury represents a target occurring within a clinically relevant therapeutic window, and as such, prevention of secondary injury represents an area of intense research effort. The duration of this therapeutic window remains unclear and varies

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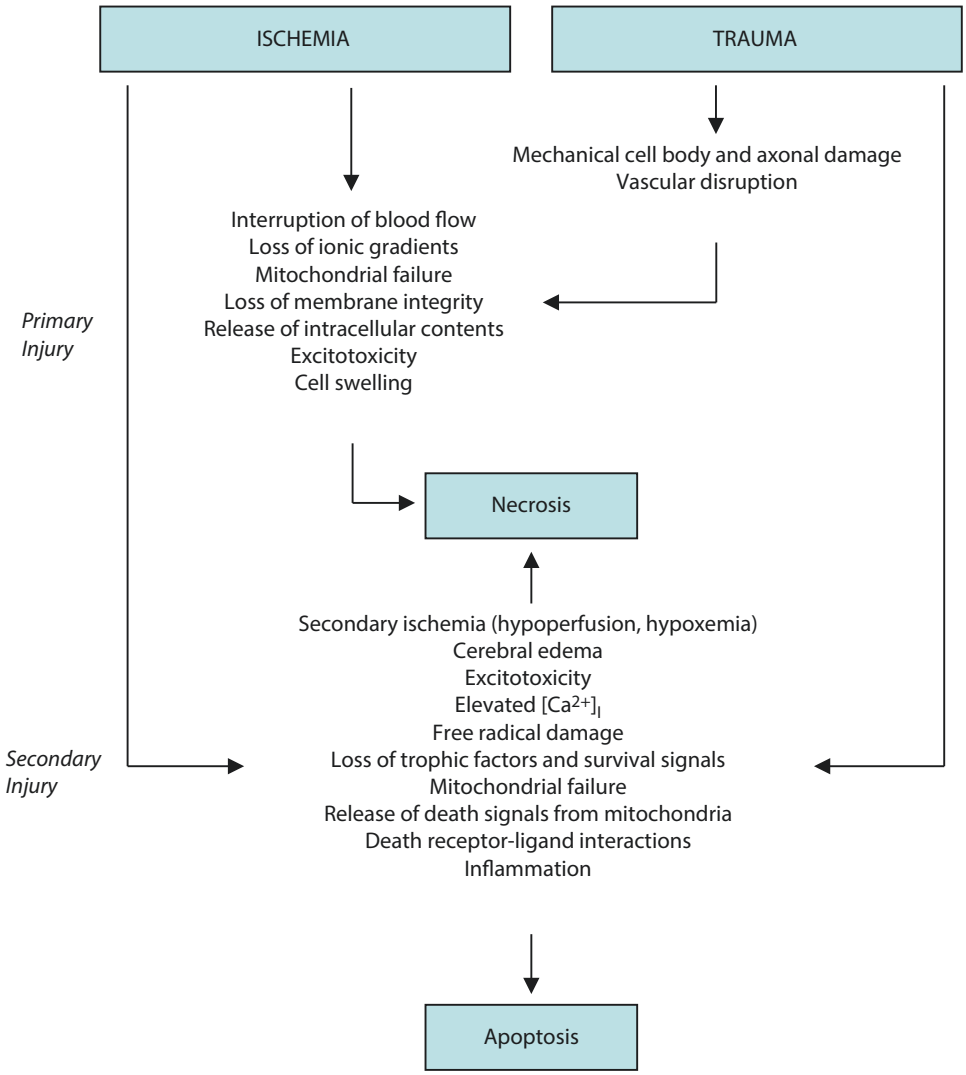

Fig. 25.1 Cascade of cellular events resulting in primary and secondary brain injury after ischemia or trauma

Typical early events after cardiac arrest: low flow → no flow → cellular hypoxia → loss of consciousness → loss of glucose and ATP stores within 5 min → ROSC → transient hyperemia → low flow.

depending upon the type of brain insult. After global ischemia, such as after cardiac arrest, a transient cerebral hyperemia occurs typically within the first several minutes after restoration of spontaneous circulation, followed by protracted global hypoperfusion lasting several days. Selectively vulnerable brain regions, including the CA1 hippocampus, basal ganglia, layers 3 and 5 of the cortex, and cerebellum, are often most severely affected. Cell death after TBI has been documented in autopsy specimens as early as 2 h post-injury, demonstrated by eosinophilic neurons, axonal swelling, glial swelling, and neutrophilic infiltration. Apoptotic cell death after TBI has been shown to evolve over 24–72 h in certain brain regions such as the cerebral cortex and hippocampus. In other brain regions cell death is more protracted, for example, neuronal death in the thalamus evolves over a period of weeks after TBI.

Primary brain injury occurs immediately and often results in necrotic cell death, while secondary injury evolves over hours to days – representing a therapeutic target.

Several etiologies contribute to secondary brain injury and recovery after TBI and hypoxic-ischemic brain injury: ischemia, excitotoxicity, oxidative stress, cerebral edema, and neuroinflammation. As will be discussed, these mechanisms are not mutually exclusive. For example, cerebral edema can contribute to ischemic brain injury, and oxidative stress is a trigger for neuroinflammation. These relationships and how they contribute to neurologic injury will be covered in the subsequent sections.

25.2.1 Ischemia

Cerebral ischemia can be due to hypotension, hypermetabolism, vascular injury, thrombi, vascular dysregulation, and vascular compression.

Cerebral ischemia, defined as inadequate delivery of oxygen and substrate to the brain to meet metabolic demand, has several causes including hypotension, thrombosis, elevated metabolic demand, vascular dysregulation, and vascular compression including as a consequence of intracranial hypertension. No- or low-flow states, seen during asystole or the period leading up to asystole, respectively, result in cellular hypoxia and depletion of energy substrates. Consciousness is lost, and oxygen stores are exhausted 20 s after normothermic cardiac arrest, while glucose and adenosine triphosphate (ATP) stores are lost within 5 min. After cardiac arrest, no-flow durations longer than 5 min are associated with irreversible cerebral ischemia. Post-insult hypoperfusion is common in both cardiac arrest and TBI patients, although a transient hyperemia may precede hypoperfusion after cardiac arrest. Cerebral blood flow (CBF) indicative of hypoperfusion is generally defined as below an ischemic threshold of 20 mL/100 g brain tissue/min. Using co-registered maps of CBF, cerebral metabolic rate for oxygen ($CMRO_2$), and oxygen extraction fraction (OEF) suggests that the ischemic threshold after TBI in humans may be as low as 15 mL/100 g brain tissue/min, differing from the threshold of 20 mL/100 g brain tissue/min defined in stroke patients.

After cardiac arrest, no-flow time durations longer than 5 minutes are associated with irreversible cerebral ischemia.

Examining the causes of cerebral ischemia listed above, hypotension and hypoxia have been the most consistently associated with worse outcomes after acute brain injury and therefore should be aggressively managed in the prehospital and hospital settings as they are often correctable. Also commonly encountered in the ICU are causes of elevated cerebral metabolic demand ($CMRO_2$ or glycolysis) leading to "relative ischemia." This can be global due to fever or generalized seizure or more focal due to CNS infection or focal seizure. In either case, $CMRO_2$ and/or glucose utilization can be massively increased in the affected areas without proportionately compensated cerebral perfusion. Ischemia may also be caused by vascular dysregulation, an imbalance in the ratio of endogenous vasoconstrictors and vasodilators. For example, after TBI there are reductions in the vasodilatory response to nitric oxide (NO), cGMP, cAMP, and prostanoids and/or increases in vasoconstrictive substances such as endothelin-1. Furthermore, in areas of traumatic hemorrhage, the potent vasodilator NO is rapidly oxidized to nitrate/nitrite, and adenosine is metabolized by adenosine deaminase released from lysed erythrocytes. Lastly, cerebral edema can also result in a vicious cycle of compression ischemia. This can be seen at the bedside when intracranial pressure (ICP) approaches mean arterial pressure (MAP). Even mild-moderate ICP spikes may cause local ischemia as evidenced by increases in local concentrations of lactate and excitatory amino acids detected in patients with microdialysis catheters.

Reperfusion injury after return of spontaneous circulation (ROSC) involves a complicated cascade of events that begins with membrane depolarization, calcium influx, NMDA activation, glutamate release, acidosis, mitochondrial dysfunction, and activation of lipases, proteases, and nucleases. This sets the stage for reoxygenation injury with cascades that involve oxygen and nitrogen radicals, iron, catecholamines and other excitatory amino acids, calcium overload, poly(ADP-ribose) polymerase activation, energy failure, mitochondrial damage, and DNA fragmentation. These processes can ultimately lead to cell death, often in a nonvascular distribution in neuronal populations that have increased susceptibility to injury after cardiac arrest.

25.2.2 Excitotoxicity

Traumatic or ischemic brain injury results in an increase of excitatory amino acids, primarily glutamate, within the CSF. High levels of glutamate can cause neuronal damage by increasing cytoplasmic calcium.

Excitotoxicity describes the process by which supraphysiologic amounts of glutamate and other excitatory amino acids produce neuronal damage. Typically, a highly regulated balance between excitatory and inhibitory inputs results in normal neurological function. After brain injury, such as from trauma or ischemia, this balance is altered and results in a predominance of excitatory amino acids, primarily glutamate. Systemic administration of toxic levels of glutamate can produce neuronal death in vivo. Glutamate concentrations above the threshold for producing neuronal damage are well described after ischemia and TBI. Increases in glutamate and other excitatory amino acids have been reported in CSF from infants and children after TBI vs. controls, and there is an independent association between increased CSF glutamate and inflicted injury from child abuse.

Elevated glutamate, in particular extrasynaptic glutamate, may lead to neuronal damage through receptor-mediated opening of NMDA and AMPA Ca^{++} channels and release of intracellular calcium stores. The increase in cytoplasmic calcium triggers multiple cell death pathways such as apoptosis, necrosis, and autophagy. Pretreatment with glutamate receptor antagonists such as phencyclidine and MK-801 improves neurological outcome after ischemia and TBI in laboratory animals. Disappointingly, clinical trials with anti-excitotoxic therapies have been unsuccessful. This may be related to study designs where therapies have been applied to all patients with TBI rather than those with excitotoxicity, treatments initiated too late (excitotoxicity may present a narrow therapeutic window), or undesirable specific or nonspecific effects of the agents tested.

25.2.3 Oxidative Stress

Oxidative stress refers to the pathologic formation of toxic free radicals leading to cellular damage and can contribute to both ischemic and post-traumatic secondary brain injury. Oxidative stress can occur early after acute brain injury and is primarily related to mitochondrial dysfunction. A key step in the process of generating free radicals is oxidation of the phospholipid cardiolipin in mitochondria by cytochrome *c* and disruption of electron transport.

The brain, particularly in children, may be more susceptible than other organs to injury due to its high oxygen consumption. An imbalance between free radicals such as superoxide, hydroxyl radicals, and reactive nitrogen species and endogenous antioxidants such as superoxide dismutase, ascorbate, glutathione, and NO may cause spontaneous or enzymatically mediated reactions between free radicals and lipids or proteins. Being ~70% composed of lipids, the brain contains a high concentration of polyunsaturated fatty acids that are released following acute brain injury and react with free radicals to undergo lipid peroxidation.

Mitochondrial-targeted antioxidant therapies have shown neuroprotective effects in pre-clinical models of ischemic and traumatic brain injury. A recent phase I trial in children with severe TBI tested the combination of the antioxidant drug N-acetyl cysteine and its adjuvant probenecid and observed detectable concentrations of N-acetyl cysteine in the CNS and no adverse effects.

25.2.4 Cerebral Edema

Brain swelling is a hallmark feature of severe TBI and is reflected clinically as intracranial hypertension.

Cerebral edema is a hallmark feature after severe brain injury. A contributory pathologic role for brain swelling is much better established after TBI compared with cerebral ischemia; however, cerebral edema may also play a detrimental role in subthreshold ischemia. Cerebral swelling and accompanying

intracranial hypertension contribute to secondary damage in at least two ways. As discussed above, intracranial hypertension can compromise cerebral perfusion through small arteries, arterioles, and capillaries leading to secondary ischemia, essentially producing intracranial "compartment syndrome." In addition, under conditions of extremely high or rapidly increasing ICP, it can produce the devastating consequences of deformation through herniation syndromes compressing major arteries choking off blood supply.

Recently, cellular pathways leading to cerebral edema as well as genetic and etiologic factors which pose a greater risk of cerebral edema have been identified. Edema in body tissues is often labeled as vasogenic or cytotoxic; however, current understanding is that pathways leading to vasogenic and cytotoxic edema are interrelated. Cellular/cytotoxic edema occurs through upregulation of ion channels which allow water influx, the most well-described channels in acute brain injury being aquaporin-4 (AQP4) and sulfonylurea receptor 1 (SUR1)-regulated ion channels. Water influx into cells can lead to oncotic cell death. Astrocyte swelling occurs during the uptake of excessive glutamate and sodium and other substances in response to injury. Glutamate uptake is coupled to glucose utilization via a sodium/potassium ATPase, with sodium and water accumulation in astrocytes. Disturbances in aquaporin proteins forming water channels may also result in excessive water accumulation in astrocytes. Swelling of neurons and other cells can also result from ischemia- or trauma-induced ionic pump failure.

Vasogenic and cytotoxic edema can both contribute to intracranial hypertension after TBI.

Vasogenic edema refers to a net influx of water across a disrupted blood-brain barrier (BBB). Cells lining the BBB, including endothelial cells and astrocytic foot processes, may be affected by all the neuronal cell death mechanisms discussed in this section. Cell death of endothelial cells and astrocytes lining the BBB will lead to BBB impairment. In addition, inflammatory cytokines and immune cells may cause breakdown of intact BBB through down-regulation and mechanical disruption of tight junctions. Lastly, there may be a decrease in the efflux of water from the CNS possibly caused by a loss of polarization of water channels at the BBB. A disrupted BBB may also contribute to edema formation in the extracellular space, particularly in contusions, secondary to sequestration of osmogenic substances such as ions, proteins, and drugs such as mannitol extravasated at a time when the BBB is disrupted, trapped after reestablishment of the BBB. As such, the role of BBB in the development of post-traumatic edema may be dynamic – particularly in the setting of cerebral contusion. One possibility is that as macromolecules from dying or dead cells are degraded within injured brain, the osmolar load in the contused tissue increases. When the BBB reconstitutes, a considerable osmolar driving force for the local accumulation of water develops, resulting in the marked swelling so often seen in and around cerebral contusions.

25.2.5 Inflammation

Neuroinflammation has been most closely studied in terms of focal ischemia and TBI. Although inflammation may cause secondary injury after ischemia or TBI, neuroinflammation also plays a critical role in repair and regenerative mechanisms after acute brain injury. Attempts to block neuroinflammation after focal ischemia or TBI with anti-inflammatory drugs, most notably corticosteroids, have failed to improve outcomes.

Neuroinflammation is often initiated in response to damage-associated molecular patterns (DAMPs) released from injured and dying cells. DAMPs are cellular components which are not normally pro-inflammatory but are

capable of producing inflammation in certain contexts, for example, extracellular DNA and RNA, cytoplasmic high mobility group box 1 (HMGB1), and lipid peroxidation-derived carbonyl adducts of proteins.

Leukocyte activation and infiltration typically begins within minutes to hours of primary brain injury with activation of resident microglial cells and recruitment of neutrophils from the circulation. This is followed by lymphocyte and peripheral monocyte recruitment to brain and meninges. These inflammatory cells, as well as resident glial cells, produce inflammatory mediators, most notably cytokines and chemokines, which typically peak within 24–48 h and decrease over several weeks. This inflammatory response is influenced by patient age, mechanism of injury, secondary insults (e.g., hypotension, hypoxia), and several therapies that are used for resuscitation and support.

Chronic inflammation may occur after TBI has been linked to dementia and neurodegenerative disorders. Autopsy specimens from patients over 1 year from traumatic injury demonstrated activated microglia in white matter tracts, and studies using PET ligands specific for activated microglia have shown that retired NFL players with multiple concussions have increased ligand binding relative to controls. Several case reports have begun to associate chronic traumatic encephalopathy (CTE) with activated microglia in patients with repetitive TBI.

25.2.6 Conclusion

Prevention of secondary injury requires early recognition and treatment of hypotension, hypoxemia, hyper/hypocarbia, hyperthermia, seizures, hyper/hypoglycemia, and intracranial hypertension.

Multimodal brain monitoring is essential for early recognition and treatment of physiologic derangements and may provide an objective basis for the prevention or mitigation of secondary brain injury. Principal targets for titration of supportive and ICP-directed therapies in the ICU are discussed in more detail below.

25.3 Neurointensive Care Monitoring

In the era of modern intensive care, invasive monitoring is generally considered standard of care. This includes continuous monitoring of arterial blood pressure, central venous pressure, temperature, carbon dioxide, and oxygenation and frequent assessment of electrolytes, serum osmolarity, and arterial blood gases. Contemporary invasive and non-invasive neuromonitors are now routinely used in many centers, all with strengths and weaknesses. These monitors if interpreted correctly provide adjunctive information that may be useful for optimizing care of the brain-injured patient, via detection of secondary brain injury or precipitators of secondary brain injury, assisting in applying treatment strategies, and/or evaluating the effectiveness of interventions – i.e., therapeutic drug (or intervention) monitoring. Normal and some critical threshold values for currently used neurointensive care monitors are shown in Table 25.1.

25.3.1 Non-invasive Monitoring

Basic bedside monitoring is also essential for severely brain-injured patients and should include serial Glasgow Coma Scale (GCS) score and neurological examinations. The neurological examination should also include pupillary

Table 25.1 Values for cerebral blood flow, oxygenation, and metabolism in adults

	Normal	Critical
Cerebral blood flow		
Global	52 mL/100 g/min	<18–20 mL/100 g/min
Cortical	80 mL/100 g/min	
Oxygenation		
Jugular venous O_2 saturation ($SjVO_2$)	55–71%	<50%
Arteriovenous O_2 difference ($AVDO_2$)	4.5–8.5 vol%	
Brain tissue pO_2 ($pbtO_2$)	20–40 mm Hg	<8.5–10 mm Hg
Metabolism		
Cerebral metabolic rate for O_2 ($CMRO_2$)	3.4 mL/100 g/min	
Cerebral metabolic rate for glucose	0.325 μmol/g/min	
Cerebral metabolic rate for lactate	−0.02 μmol/g/min	
Extracellular fluid glucose concentration	1.7 μmol/L	
Extracellular fluid lactate concentration	2.9 mmol/L	
Extracellular fluid pyruvate concentration	166 mmol/L	

Adapted from Robertson and Hlatky (2005) – see Suggested Readings

and cranial nerve examination. These should be performed by multiple observers including bedside ICU nurses, critical care physicians, neurosurgeons, and/or neurologists. Training of new staff and interval assessment of these simple monitoring measures to reduce inter-observer variability and improve consistency and reliability are valuable. Clinical examination is much more imperative when ICP, continuous EEG, or other brain monitoring are not utilized.

The Glasgow Coma Scale score is modified for infants and consists of the following elements:

Eye opening
4 Spontaneous
3 To speech
2 To pain
1 None
Verbal response
5 Coos, babbles
4 Irritable
3 Cries to pain
2 Moans to pain
1 None
Motor response
6 Normal movements
5 Withdraws to touch
4 Withdraws to pain
3 Abnormal flexion
2 Abnormal extension
1 Flaccid

25.3.2 Intracranial Pressure

Although no modality specific for neuromonitoring has yet to be validated by large, randomized, clinical trials, invasive monitoring of ICP for TBI patients is considered standard of care. Increased ICP is defined as >20 mm Hg (resting normal 5–10 mm Hg). This threshold is based on a compilation of studies identifying 20 mm Hg as a cutoff for identification of poor outcome. Specifically, causality was not shown, but clear associations were detected between ICP >20 mm Hg and mortality. Importantly, elevated ICP can be inferred, but cannot be definitively determined clinically, by computerized tomography (CT) scan of the head, or by other currently available non-invasive monitors. Consensus was drawn from adult data regarding which patients are most at risk for raised ICP and should receive ICP monitoring: either GCS score 8 or less, an abnormal CT scan (hematoma, contusion, cerebral edema, compressed basal cisterns), or rapidly declining level of consciousness. Currently available ICP monitors, defined by where the catheter tip is placed and the mode of pressure measurement, include ventricular, subarachnoid, epidural, subdural, and parenchymal placement and fiberoptic strain gauge and pressure transducer-based systems. Advantages of the extraventricular drain catheter are low cost, straightforward design (fluid column and pressure transducer), ease of recalibration, and the capacity to drain CSF as a mode of therapy. Complications regardless of device are rare and include infection (1–10% of cases) and hemorrhage (1–2%). Currently the only major contraindication is severe uncorrected coagulopathy. In the era of "goal-directed therapy," it is generally recommended that therapeutic interventions be targeted to achieve an ICP <20 mm Hg.

A GCS score ≤8 is considered an absolute indication for ICP monitoring after TBI.

In cardiac arrest, ICP-directed strategies bundled with other interventions such as steroids, hypothermia, and hyperventilation in children who drowned were reported decades ago. This approach was abandoned, however, when increased survival with poor neurological outcome with increased risk of adverse events was identified.

The critical threshold value for ICP is 20 mm Hg.

25.3.3 Cerebral Perfusion Pressure

Autoregulation refers to the process of maintaining CBF across a range of CPP.

Cerebral blood flow is normally maintained across the physiologic range of cerebral perfusion pressure (CPP) – a process referred to as autoregulation. CPP can be readily determined when ICP is measured as the difference between mean arterial pressure (MAP) and ICP (or central venous pressure, whichever is greater). When autoregulation is intact, cerebral arteries and arterioles adjust their diameter based on CPP to maintain CBF (◘ Fig. 25.2). When CPP increases, cerebral blood vessels constrict, and when CPP decreases, cerebral blood vessels dilate. Since CBF is proportional to the driving pressure and inversely proportional to the resistance of the vessel, and resistance is inversely proportion to the radius of the vessel through which blood is flowing, CBF is maintained constant. Both below the lower limit of autoregulation and above the upper limit, CBF is "pressure passive." In other words, at low and high CPP, CBF correlates directly with CPP, increasing or decreasing in parallel with changes in CPP. The normal autoregulatory range for adults is approxi-

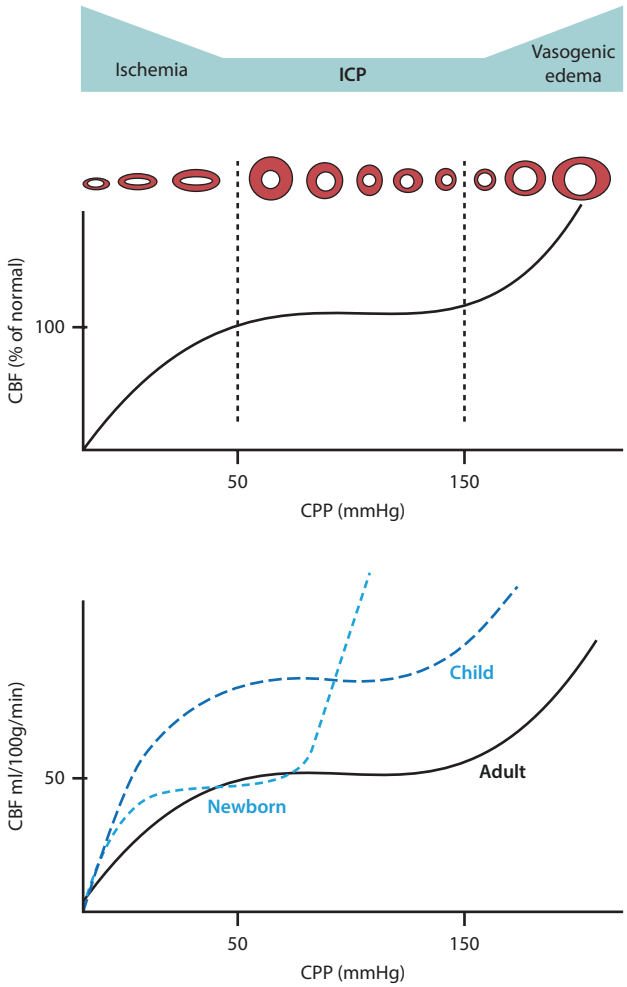

Fig. 25.2 Cerebral blood flow (*CBF*) – blood pressure autoregulation. CBF is generally maintained at a constant level throughout the physiologic ranges of cerebral perfusion pressure (*CPP*). Ranges below and above the autoregulatory curve can result in changes in cerebral blood volume (*CBV*), which can translate into increased intracranial pressure (*ICP*). The autoregulatory curve changes with age

mately a CPP between 50 and 150 mm Hg. It stands to reason that the autoregulatory range for children would be shifted as ranges for normal MAP and CBF shift with age (Fig. 25.2).

The threshold value for critically low CPP after TBI has been estimated to be 60 mm Hg in adult patients. This value is based on accumulated data from multiple studies demonstrating an association between poor outcome and CPP <60 mm Hg. Age-related differences also exist in the specificity of ICP and CPP in the first 6 h after severe TBI for predicting outcome. Common practice typically assigns CPP thresholds of 60, 50, and 40 mm Hg for adolescents, young children, and infants, respectively, although evaluation of CPP thresholds associated with poor outcome support a value of 40 mm Hg for children of all ages. This issue is made complicated by studies showing that hypotension after TBI (to MAP below 50–60 mm Hg even if ICP was normal) is one of the most powerful harbingers of poor outcome and studies suggesting that CPP thresholds may even be higher in children than in adults, possibly related to higher normative CBF. Low CPP after brain injury can result in regional cerebral ischemia if profound, below the ischemic threshold, and regional ischemia

Cerebral Perfusion Pressure

CPP = MAP – ICP

if CVP > ICP, use CVP in place of ICP

CPP = MAP – CVP

Critical CPP after TBI in adults and adolescents, young children, and infants is 60, 50, and 40 mm Hg, respectively.

Increased time spent with ICP > 20 mm Hg and CPP < 45 mm Hg is associated with poor outcome in pediatric TBI.

in-and-around injured brain when global CBF is near but above the ischemic threshold. Ischemia as discussed above is an important cause of secondary brain injury. Accordingly, continuous assessment of CPP is a valuable means of detecting risk for secondary brain injury and is useful for its prevention and treatment if it occurs.

The amount of time a pediatric patient with TBI spends above a critical ICP threshold (>20 mmHg) is associated with poor outcome. The odds for poor outcome increase by 4.6% for every hour spent with an ICP >20 mm Hg. The time a pediatric patient with TBI spends with a CPP <40 mm Hg is also associated with poor outcome. Cumulative time above ICP or below CPP thresholds and associations with poor outcome were not found to be dependent upon accidental versus abusive mechanism of injury. It is important to note, however, that thresholds defined in pediatric guidelines based on pediatric studies represent minimum values below which associations with unfavorable outcome are seen. Higher CPP, or lower CPP, may need to be the clinical bedside target to avoid breaching the threshold.

25.3.4 Cerebral Blood Flow

Cerebral blood flow can be measured directly using techniques such as stable xenon computerized tomography (CT), intravenously injected radioactive xenon with external detectors, positron emission tomography (PET), perfusion MRI, or the Kety-Schmidt technique. Up until the late 1990s, the most widely available and user-friendly method for quantifying regional and global CBF values in humans was stable xenon CT. A mandate by the Food and Drug Administration (FDA) shelved stable xenon CT until safety could be established, however, resulting in the inability to use xenon CT studies not directly related to safety evaluation or as part of a research study with informed consent obtained. As such, surrogate measures reflecting CBF in humans have been more frequently applied.

For adults, global CBF of 50 mL/100 g brain tissue/min is considered normal. Normal values for CBF are age dependent (Fig. 25.3) with a nadir in newborn infants of approximately 40 mL/100 g brain tissue/min. CBF peaks around 4 years of age to values of approximately 80 mL/100 g brain tissue/min, declining to adult values during adolescence. As mentioned above, existing studies support a critical value for low CBF of <20 mL/100 g brain/min for any age patient. Like CPP, threshold values may vary depending upon the age of the patient, particularly in the 4–8-year-old patient, where normal CBF values are more than double the adult norms, and in newborns and very young infants, where CBF values are below adult norms.

Normal CBF is age-dependent, peaking at 4 years of age.

Critically low CBF which can result in irreversible brain damage is <20 mL/100 g brain/min in adults.

In children following pediatric cardiac arrest who underwent brain MRI within 2 weeks of the event, regions of increased CBF on arterial spin-labeling brain MRI correlated with regions with diffusion-weighted lesions consistent with cytotoxic edema, a condition associated with poor outcome. These findings may assist in uncovering more information regarding pathophysiology and potential interventions.

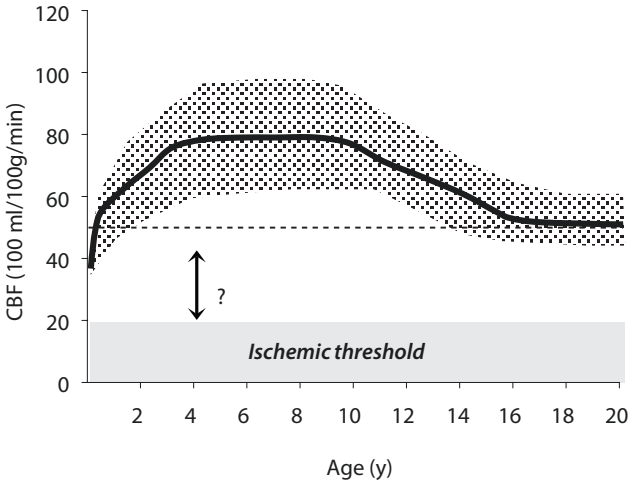

Fig. 25.3 Age dependency of cerebral blood flow (*CBF*). It is not known whether the ischemic threshold, defined as 20 mL/100 g brain/min in adults, is also age dependent

25.3.5 Transcranial Doppler Ultrasonography

TCD non-invasively and indirectly assesses CBF via middle cerebral arterial blood flow velocity.

Cerebral blood flow can be indirectly assessed using transcranial Doppler (TCD) ultrasonography. It is a non-invasive, bedside method that measures middle cerebral arterial blood flow velocity as a surrogate for CBF itself. This technique correlates with CBF measured with xenon CT. The non-invasive nature of the technique is its biggest advantage. Disadvantages include the inability to translate CBF velocity to flow and possible discrepancies between middle cerebral artery "flow" and regional CBF, particularly in heterogeneous insults such as TBI. Changes in CBF velocity can be tracked within individual patients, however, and can be useful particularly when instituting interventions that may affect global CBF, e.g., hyperventilation. TCD has been used in assessing stroke risk in patients with sickle cell disease, after TBI to estimate ICP, after birth asphyxia to predict neurological outcome, and it has been demonstrated that abnormal cerebral autoregulation precedes cerebral edema in children presenting with diabetic ketoacidosis and altered mental status. In a series of adults with cardiac arrest, delayed hyperemia, defined as high middle cerebral artery blood flow velocity on TCD, was associated with brain edema and poor outcome. In a small study of children receiving hypothermia following cardiac arrest, both reversal of diastolic flow and undetectable flow patterns during hypothermia were associated with poor prognosis. During rewarming, normal mean flow velocity and in both hypothermia and rewarming phases a normal pulsatility index were associated with good outcome. Studies validating these methods for prognostication and potential response to CBF interventions are lacking.

25.3.6 Cerebral Metabolic Monitoring

Cerebral blood flow is normally tightly coupled to metabolism and can be determined using PET or calculated by the product of CBF and oxygen or substrate (mainly glucose) extraction. For example, cerebral metabolic rate for oxygen can be calculated by the following formula:

$$CMRO_2 = CBF \times AVDO_2$$

where

$$AVDO_2 = CaO_2 - SjvO_2$$

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For the most part, patients in the ICU have arterial oxygen saturations near 100% reflecting the primary contribution to arterial oxygen content (CaO_2). Thus, the arteriovenous oxygen difference ($AVDO_2$) is influenced mostly by jugular venous oxygen saturation ($SjvO_2$). Currently, CBF can only be directly measured intermittently, if at all. Accordingly, monitoring of $SjvO_2$ may provide a bedside estimate of the balance of global oxygen delivery and cerebral metabolism. Jugular venous oxygen saturation can be continuously measured with an internal jugular vein fiberoptic catheter placed cephalad into the jugular bulb.

Low $SjvO_2$ (<50%) can be secondary to increased ICP, hypoxemia, hypotension, and/or anemia and correlate with poor outcome after TBI.

Normal values in adult males range from 55% to 71%, and critical values suggestive of brain tissue ischemia are felt to be <50%. Critically low $SjVO_2$ can be secondary to increased ICP, systemic hypoxemia, hypotension, anemia, or a combination of these. $SjvO_2$ < 20% can be indicative of irreversible ischemic injury. High $SjVO_2$ values indicate that cerebral oxygen delivery exceeds consumption, as a result of either increased CBF, referred to as "hyperemia"; reduced metabolism, an extreme example would be as in the case of brain death; or an uncoupling of CBF and metabolism. Some studies found that $SjvO_2$ did not substantially influence patient management above and beyond systemic ICP monitoring. There are also considerations in terms of laterality, where bilateral placement of jugular venous catheters can often yield significant variance between right and left jugular bulb catheters drawn simultaneously in the same patient. Complications in children related to $SjvO_2$ monitoring are carotid artery puncture, catheter malposition, and bacterial colonization with and without bacteremia. However, $SjvO_2$ monitoring may be useful in predicting outcome, given that multiple $SjvO_2$ desaturations are associated with poor neurological outcome. The occurrence of high $SjvO_2$ does not appear to influence outcome. Nonetheless, $SjvO_2$ can provide a useful adjunct to other neurointensive care monitoring devices, particularly in complicated patients where second-tier therapies for refractory intracranial hypertension are considered. For example, $SjvO_2$ monitoring may help direct therapies such as hyperventilation as one can reduce the degree of hyperventilation if $SjvO_2$ drops below critical thresholds.

High $SjvO_2$ (> 70%) may represent uncoupling of CBF and metabolism or "hyperemia."
$CMRO_2 = CBF \times AVDO_2$

Global CMRGlu is generally decreased after TBI, although regional increases suggestive of "hyperglycolysis" can be seen.

Similar to cross-brain utilization of oxygen, cross-brain utilization of glucose (and any other metabolites) can also be measured when a jugular venous catheter is in place. Coupled with measurement of CBF, cerebral metabolic rate for glucose (CMRGlu) can be calculated. While the utility of CMRGlu in brain-injured patients is far less understood than $CMRO_2$, global CMRGlu is generally depressed after TBI and ischemia, similar to $CMRO_2$. Since heterogeneous patterns of injury, CBF, and metabolism can occur after TBI, interpreting global measurements of CMRGlu, and $CMRO_2$ for that matter, can be problematic. Regional increases in glucose utilization have been observed in TBI patients using positron emission tomography (PET) scanning, often to values felt to be consistent with "hyperglycolysis."

In children with severe traumatic brain injury, two or more measurements of $SjvO_2$ < = 55% were associated with a poor neurologic outcome. Further studies are needed to recommend the use of these variables as a guideline to optimize treatment.

25.3.7 Brain Tissue Oximetry

Brain oxygenation can be measured using near-infrared spectroscopy (NIRS), a non-invasive technology developed in the 1970s, in which sensors are placed on the forehead. NIRS utilizes light in the near-infrared spectrum (700–1000 nm wavelength), which can penetrate bone, tissue, and muscle. The light

travels in an elliptical motion superficially (through skin and bone) or deeper (through skin, bone, brain tissue, blood vessels) and is sensed at the proximal and distal detector, respectively. The absorption of light by chromophores, oxyhemoglobin, deoxyhemoglobin, myoglobin, and cytochrome C oxidase, at the proximal and distal detectors, allows for calculation of regional cerebral oximetry (rScO2). NIRS technology with regard to light sources and wavelengths, detectors, and oxygenation calculation algorithms vary across devices; therefore, rScO2 values may differ based on the equipment utilized. NIRS does not differentiate between pulsatile flow; therefore, the measurements obtained reflect mixed blood, with the majority (70–85%) being comprised of venous blood. Oftentimes, the oximetry value compared to baseline or trend over time has been felt to be more informative than an absolute value.

Cerebral tissue oxygenation as measured by NIRS has been shown in children to correlate with SvO2 and SjO2. The main advantages of NIRS are that the technique is non-invasive and provides a continuous readout. It has been widely adopted during pediatric cardiac surgery, to alert physicians of intraoperative changes in cerebral oxygenation, and to predict neurological outcomes. Current disadvantages include relatively limited depth of penetration of the readout (millimeters), which can be impacted by scalp edema or the presence of hematomas, light disruption due to skin or hair pigmentation and hyperbilirubinemia, global rather than focal information, and lack of definitions in terms of target and critical values.

Brain tissue oxygenation can be measured non-invasively using NIRS.

However, measurement of continuous oxygen saturation on the brain surface can provide relative real-time alterations in brain oxygenation, which can be useful in terms of titration of therapies. NIRS performed in the first 48 h after neonatal asphyxia measuring cerebral oxygen saturation and fractional tissue oxygen extraction is predictive of outcome at 3 months. Similarly, in adults with cardiac arrest with ROSC, initial and mean rScO2 are associated with survival to discharge and favorable neurological outcomes. More recently, NIRS monitoring has been utilized to detect ROSC following cardiac arrest. NIRS also detects changes in cerebral hemodynamics in pediatric TBI patients, correlating with events such as ICP spikes and seizures, and is being trialed for detection of traumatic intracranial hematoma. In a study of 10 children with severe TBI, hyperventilation resulted in cerebral oxygen desaturation. The correlation between ICP and NIRS was not as strong; however, elevated ICP often correlated with an increase in oxyhemoglobin suggesting cerebrovascular dilatation and an increase in cerebral blood volume. The specific placement of NIRS monitors in a patient with TBI may significantly impact the signal, for example, if the optical fibers were placed on the skin overlying an intracranial hematoma. The effect is so significant that in a case-control study of children with CT imaging, it was demonstrated that NIRS could correctly identify all cases of intracranial hemorrhage.

Measurement of brain tissue oxygen partial pressure ($PbtO_2$) using a separate probe inserted directly into the brain is another invasive way of estimating alterations in CBF and metabolism after brain injury. These fiberoptic catheters measure dissolved oxygen tension and are also capable of measuring temperature, carbon dioxide, and pH. Normal values of $PbtO_2$ are 20–40 mm Hg, and pediatric TBI literature supports a threshold of 10 mm Hg, below which studies have reported a correlation between $PbtO_2$ and poor outcome. Optimal placement of the sensor is somewhat controversial, but valuable information may be gained when the tip of the catheter is placed in viable tissue at risk for irreversible damage, or the penumbra. Alternatively, the sensor could be placed in "normal" brain distant from contusions to provide an estimate of global brain oxygenation. Most experts agree only on avoiding placement of the sensor into the center of a contusion as monitoring $PbtO_2$ in dead tissue would be misleading.

In a single-center observational study in pediatric TBI, a PbO_2 of 30 mm Hg was associated with the highest sensitivity/specificity for good neurological outcome at 6 months. However, CPP was the only factor independently associated with good outcome in multivariate analysis, and higher targets for PbO_2 remain controversial.

Brain tissue oxygenation can be measured invasively using a $PbtO_2$ monitor. Normal values = 20 – 40 mm Hg in adults.

$PbtO_2$ monitoring in an experimental model of asphyxia cardiac arrest demonstrated regional differences in tissue oxygenation: early cortical hypoxia and thalamic hyperoxia. Tissue oxygenation could also be manipulated with supplemental oxygen and blood pressure augmentation, showing the potential application as a clinical tool, with the caveat that only cortical $PbtO_2$ and not subcortical $PbtO_2$ can feasibly be interrogated.

25.3.8 Cerebral Microdialysis

Brain glucose, lactate, drug levels, and markers of tissue injury can be measured using a microdialysis catheter.

Cerebral microdialysis uses intermittent or continuous sampling of extracellular fluid to measure changes in brain chemistry and is based on the diffusion of water-soluble substances through a semipermeable membrane. It involves insertion of a fine catheter in the brain that has a dialysis membrane perfused with physiologic solution at low flow provided by a precision pump. Most experience examines molecules which are diffusible below 20,000 Da; however, larger molecules up to 100,000 Da may be measured depending upon the cutoff size of the semipermeable membrane. Assays are employed to analyze dialysate for molecules such as glucose, lactate, neurotransmitters, drugs, and markers of tissue damage and inflammation. Currently microdialysis in the brain is being utilized primarily as a research tool, and its place as a point-of-care monitor in the clinical setting remains to be seen. The potential use of this tool for brain-specific therapeutic drug monitoring warrants further investigation.

25.3.9 EEG

EEG is an essential neuromonitor when using barbiturate-induced coma.

An electroencephalogram (EEG) is a processed summation of excitatory and inhibitory post-synaptic potentials of cerebral cortex electrical activity, displayed in multiple channels. Information about frequency, amplitude, and location of focal or generalized activity can be attained using continuous EEG monitoring. This is useful in brain-injured patients in terms of detecting non-clinical seizures or seizures in patients receiving muscle relaxants as part of a clinical protocol. Continuous EEG monitoring also has an important role when using high-dose barbiturates for either status epilepticus or refractory intracranial hypertension to achieve burst suppression, since administering barbiturates beyond isoelectricity will result in undesirable cardiovascular side effects without further suppression of brain metabolism.

EEG has been used to predict outcome after TBI and cardiac arrest in pediatric patients. Seizures following cardiac arrest and TBI pediatric patients are common and may impact patient outcomes. In children who survived for 24 h or longer after cardiac arrest, a discontinuous EEG, presence of epileptiform spikes, or discharges were associated with poor outcome. In general, seizures following cardiac arrest and occurrence of certain EEG background details were also associated with outcome. Somatosensory evoked potentials (SSEPs) also have been demonstrated to possess adequate sensitivity for predicting unfavorable outcome. Prospective assessment of continuous EEG is warranted in the pediatric ICU. Incidence of seizures after TBI or cardiac arrest can approach 30–70%

25.3.10 Computed Tomography

Brain CT scan can be "normal" immediately following cardiac arrest.

Head CT is often the first choice of imaging modality after TBI or cardiac arrest since it is a readily available and rapid test (Fig. 25.4). Head CT after TBI is indicated whenever there is a concern for moderate to severe TBI and has value in detecting skull fractures, extra-axial hematomas, and parenchymal brain injury. Head CT is an important element in making the decision of whether or not ICP monitoring may be warranted and thus greatly assists in patient management. After mild TBI, the prevalence of intracranial CT scan abnormalities is 5–30% in patients presenting with a GCS score ≥ 13. About 1% of all patients diagnosed initially with mild TBI require neurosurgical intervention. The reliability of skull fracture detected using plain films to detect intracranial lesions is poor. Relationships between CT scan characteristics and outcome after TBI have been reported, although this can prove difficult considering the heterogeneity of intracranial and extracranial injuries, as well as differences in mechanism of injury and development when considering children. There appears to be good correlation between "reversal sign" (diffusely decreased density of cerebral cortical gray and white matter with a decreased or lost gray-white matter interface in contrast to the relatively greater density of the cerebellum and basal ganglia) and poor outcome in pediatric patients with TBI and hypoxic-ischemic encephalopathy. The utility of a repeat head CT scan within 24–36 h after admission in pediatric patients with moderate to severe TBI is unlikely to yield any change in therapy unless clinically indicated. Indications include significant clinical change to rule out new hemorrhage, progressive hemorrhage or herniation. Repeat CT scanning maybe required for verification of placement of invasive monitoring devices.

After hypoxic-ischemic injury, a normal initial CT scan is common in most comatose patients and does not reliably predict neurological outcome. On the other hand, an abnormal initial or follow-up CT such as loss of gray-white matter differentiation and basilar cistern and sulcal effacement indicate higher probability of an unfavorable neurological outcome. Therefore, the role of head CT after cardiac arrest, drowning, or other injuries associated with cerebral ischemia is limited to ruling out trauma or intracerebral hemorrhage as a cause of the cardiac arrest.

25.3.11 Magnetic Resonance Imaging/Spectroscopy

Brain MRI is sensitive in detecting ischemic injury.

Compared with head CT, brain MRI is more sensitive for all brain lesions except skull fracture and subarachnoid hemorrhage, but has a significantly longer scanning time and often requires sedation and/or muscle relaxants, and other neuromonitoring devices need to be MRI compatible. MRI after brain injury not only provides structural assessment but can also be used for the measurement of CBF and cerebral blood volume (CBV) and can be used to detect edema and potentially "penumbral" tissue or tissue at risk (Fig. 25.4h). In hypoxic-ischemic injury, a scoring system has been developed for infants that correlates neurological examination with MRI to predict outcome. Lesions in the basal ganglia on conventional MRI and brain lobes on diffusion-weighted imaging within the first 2 weeks after cardiac arrest represent a group with increased risk of poor outcome.

The addition of MR spectroscopy (MRS) allows for the quantification of metabolites such as lactate, pyruvate, glutamate, phosphocreatine, and N-acetylaspartate. Infants with inflicted TBI have elevated lactate by MRS suggesting hypoxic-ischemic in addition to TBI, and these patients had worse neurological outcome. MRS has been used as a predictor of neurological out-

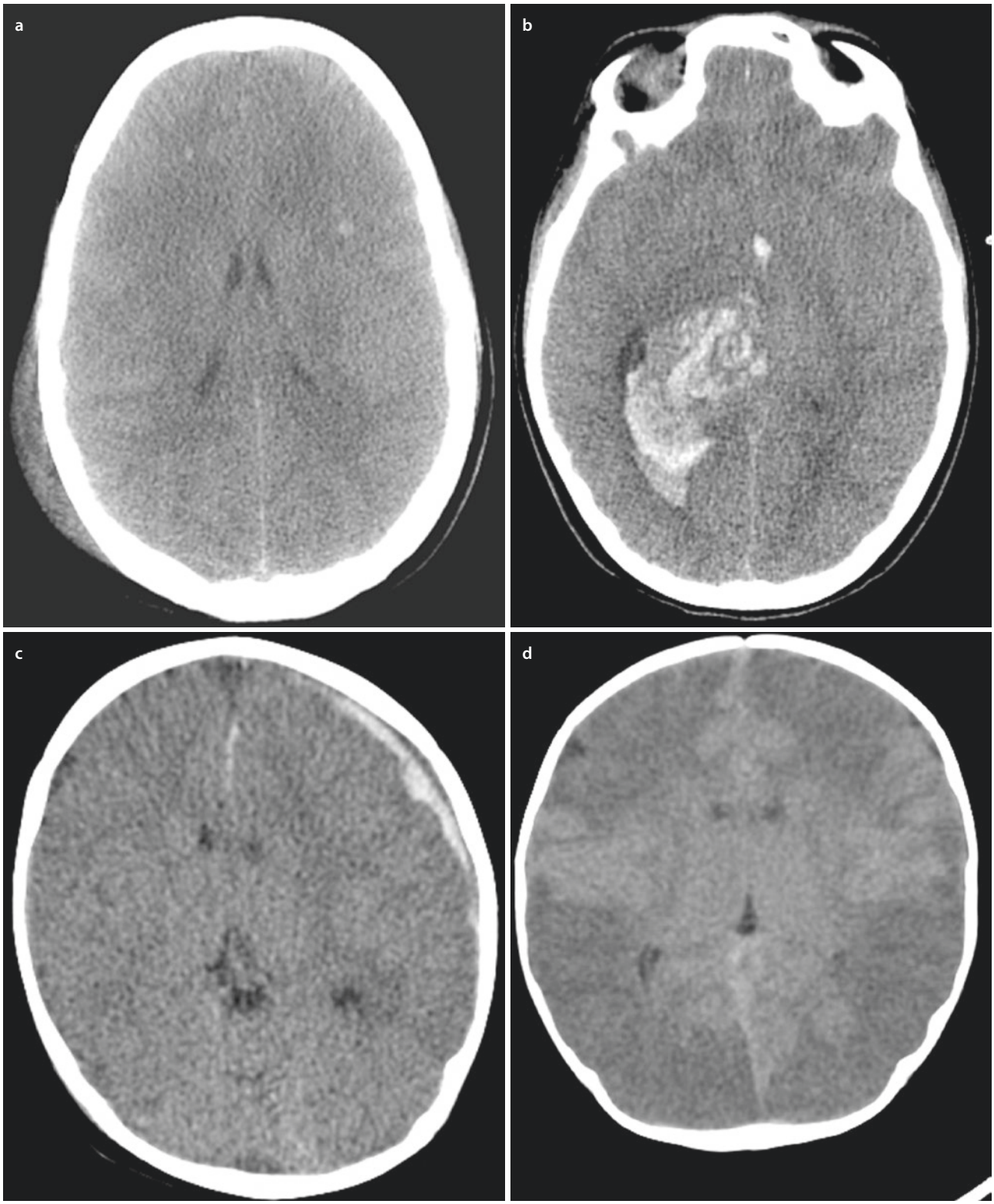


Fig. 25.4 Head computerized tomography (CT) and brain magnetic resonance imaging (MRI) studies. **a** Diffuse axonal injury in a 14-year-old after a motor vehicle accident. CT scan on arrival was negative for intracranial pathology. The patient's GCS score declined from 10 to 8 warranting this repeat CT scan. There are bilateral multifocal patchy hyper-densities at the *gray-white* junction and in *white* matter and right parietal soft tissue swelling. **b** A large right thalamic and intraventricular hemorrhage surrounding a mass lesion in a 9-year-old who presented with headache and seizures. **c** Acute left convexity subdural hematoma with mass effect extending into the interhemispheric fissure in an 8-month-old. **d** Severe, diffuse cerebral edema in a 6-week-old with non-accidental head trauma. **e** Penetrating TBI with foci of

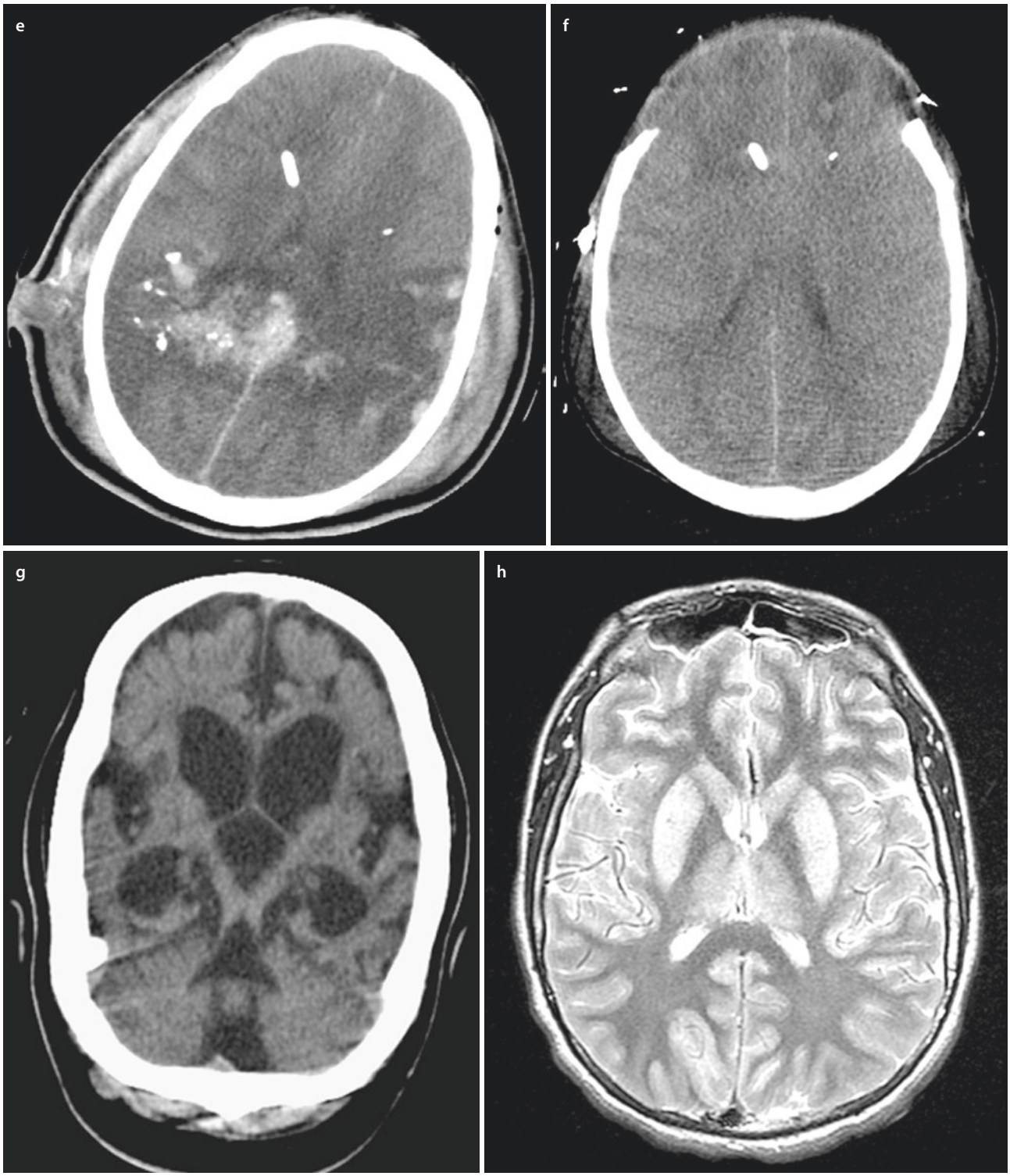


Fig. 25.4 (continued) intraparenchymal hemorrhage and significant surrounding edema bilaterally. In addition, there are subdural hemorrhage, scattered subarachnoid hemorrhage, and bilateral parietal bone fractures. A right-frontal EVD is in place. **f** A 12-year-old patient after motorcycle accident who required bilateral frontal craniectomies for refractory intracranial hypertension. There is diffuse edema with ischemic changes and decreased *gray-white* differentiation. Note the EVD on the right and a $PbtO_2$ monitor probe on the left. **g** Chronic changes after severe hypoxic-ischemic encephalopathy showing significant atrophy and ventricular dilatation. **h** Early hypoxic-ischemic encephalopathy. Brain MRI 1 week after a 25-min out-of-hospital cardiac arrest in a 17-year-old patient showing hyperintense T2 signal within the bilateral occipital lobes, basal ganglia, and perirolandic regions as well as cytotoxic edema in bilateral occipital lobes and putamen consistent with anoxic injury

come in children after brain injury. MRI in combination with MRS after severe perinatal asphyxia is felt to be powerfully predictive of neurological outcome. Lactate levels can remain elevated up to 1 week or longer after asphyxial insult in children and are associated with poor outcome.

25.4 Clinical Management Guidelines

25.4.1 Traumatic Brain Injury

25.4.1.1 Acute Management

Indications for intubation after TBI include GCS score ≤8, deteriorating level of consciousness, shock, lack of cough or gag, respiratory insufficiency, or to facilitate CT scan.

Management of the patient with TBI begins with the "ABCs" (Airway-Breathing-Circulation) of resuscitation in order to minimize and/or prevent secondary brain injury (Fig. 25.5). It is important to first confirm or obtain an open airway. Cervical spine precautions should always be observed, given that approximately 8% of patients with TBI may also have cervical spine injuries. Indications for endotracheal intubation include a GCS score of <8, deteriorating level of consciousness, lack of airway protective reflexes, respiratory insufficiency or failure, cardiovascular instability, or to facilitate obtaining CT scans. If intubation is warranted, careful choice of medications prior to intubation and the use of cricothyroid pressure (Sellick maneuver) to prevent overdistension of the stomach and aspiration are imperative. Oral (vs. nasal) endotracheal intubation and the use of sedation and neuromuscular blockade are generally recommended for pediatric patients in order to shorten procedure time and increase intubation success rate. Neuromuscular blocking agents and sedatives are indicated for all TBI patients undergoing intubation except for those where airway difficulties are anticipated (such as patients with facial or laryngotracheal trauma) or those presenting in cardiac arrest. The choice of neuromuscular blocking agents and sedatives is typically institution dependent.

CBF changes by ~3% for every mm Hg change in $PaCO_2$.

Hyperventilation reduces CBF rapidly and can be used to emergently reduce ICP.

Control of oxygenation and ventilation are the next goals in the acute management of TBI patients. The target for $PaCO_2$ between 35 and 40 mm Hg. Typically, CBF is tightly regulated by $PaCO_2$ – the loss of CO_2 reactivity is seen in only the most severely injured patients. Generally, CBF changes by 3% for every mm Hg change in $PaCO_2$, increasing as $PaCO_2$ increases and vice versa (Fig. 25.6). Accordingly, changes in CBF can result in increased cerebral blood volume (due to cerebrovasodilation) and increased ICP. If intracranial compliance is low, as may be seen particularly early after TBI, moderate increases in $PaCO_2$ could result in herniation. In contrast, hyperventilation leading to hypocarbia could result in reduced CBF at a time when CBF is generally low after TBI, with the potential for exacerbating ischemia. Epidemiologic data support maintenance of $PaCO_2$ above 32 mm Hg, since adult patients after TBI maintained at a $PaCO_2$ of 32 mm Hg had accelerated neurological recovery compared with those maintained at a $PaCO_2$ of 28 mm Hg. However, while blanket use of hyperventilation after TBI is contraindicated, it is an effective means of rapidly reducing ICP and therefore should be used when herniation is impending or ongoing. Hyperventilation can also be used as a second-tier therapy for refractory intracranial hypertension but should be monitored closely using a means for detecting ischemia induced by hypocarbia, such as measurement of CBF, $PbtO_2$, or $SjvO_2$.

Oxygenation should also be controlled after TBI. The relationship between PaO_2 and CBF is shown in Fig. 25.6. CBF is generally not regulated by oxygen concentration when PaO_2 is >60 mm Hg, whereas PaO_2 < 60 result in profound increases in CBF to offset ischemia. Potential mediators include adenosine, nitric oxide, and acidosis that are produced during times of ischemia.

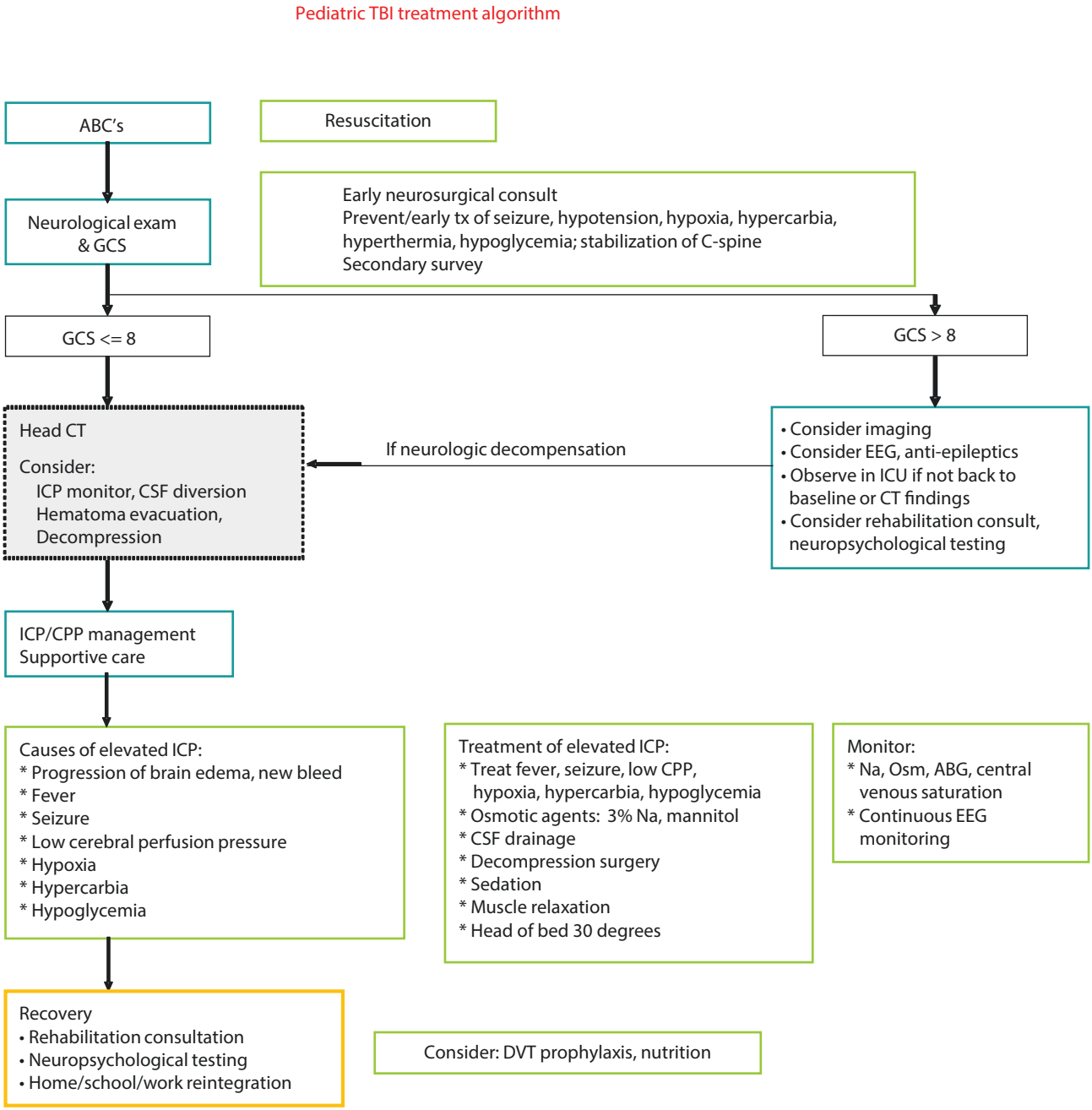


Fig. 25.5 Algorithm for the treatment of severe traumatic brain injury based on the practice and experience at the Children's Hospital of Pittsburgh

As such, hypoxemia should be avoided not only because it directly contributes to ischemia related to decreasing oxygen content but also because profound hypoxemia can result in increased CBF, CBV, and ICP resulting in compression ischemia further reducing oxygen delivery to the injured brain. Epidemiologic data support maintenance of PaO_2 above 60 mm Hg, since hypoxemia in both pediatric and adult patients after TBI is associated with poor outcome. Interestingly, hyperoxia after TBI is controversial. Both normobaric and hyperbaric hyperoxia have been proposed as potential therapies after TBI in humans. However, theoretical disadvantages to hyperoxia exist related to exacerbating oxidative stress – felt to be a prominent mechanism of second-

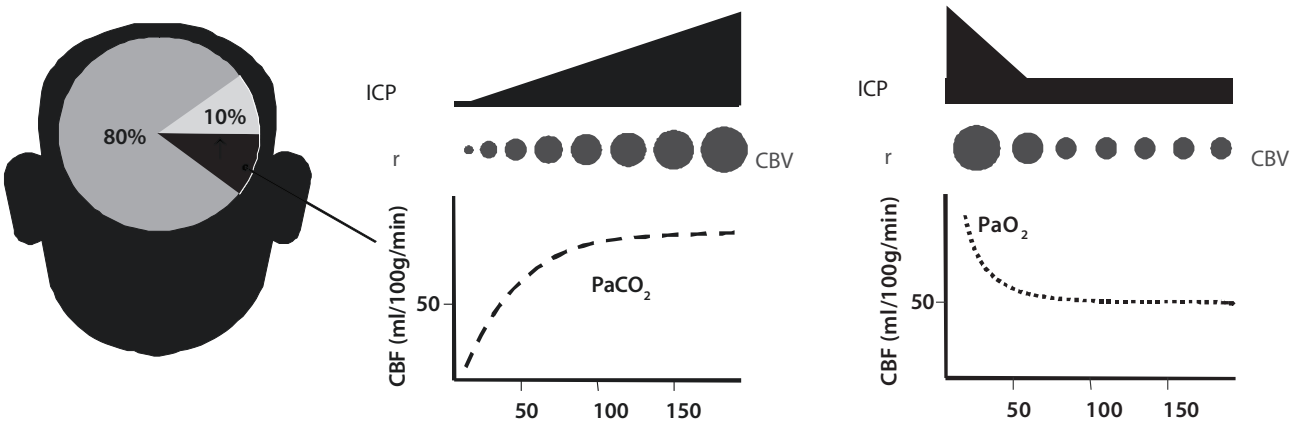


Fig. 25.6 Cerebral blood flow (*CBF*) – carbon dioxide ($PaCO_2$) and oxygen (PaO_2) reactivity curves

ary injury after TBI already. In fact, hyperoxia is now avoided in neonatal resuscitations. At this point in time, it is probably prudent to carefully titrate FiO_2 to maintain a PaO_2 target of 90–100 mm Hg around 100 mm Hg.

Hypotension is a powerful predictor of poor outcome after TBI.

Circulation is assessed for evidence of adequate perfusion in order to prevent end-organ dysfunction, including the brain. The physiologic basis for maintenance of blood pressure after TBI has been discussed above. Epidemiologic data support prevention of hypotension after TBI, since hypotension is a powerful predictor of poor outcome in both adults and children. The upper limit of blood pressure after TBI is unclear. After brain injury, hypertension may be an endogenous response to hypoperfused brain and an attempt to improve perfusion. Indeed, optimal blood pressure after TBI is currently undefined. Epidemiologic studies have shown a relationship between maximum systolic blood pressure ≥135 mm Hg and survival after pediatric TBI. In fact, induced systemic hypertension can be used as a treatment for refractory intracranial hypertension with the caveat that autoregulation must be intact. Currently, it is recommended that the temptation to treat hypertension be avoided, unless there is uncontrolled hemorrhage or values are outside the theoretical blood pressure autoregulatory curve for age.

Cushing's triad = bradycardia, hypertension, and Cheyne-Stokes respiration.

Next, a neurological examination should be performed, including reassignment of GCS score and evaluation of pupils, as part of the secondary survey. Patients with severe (GCS <8) or moderate (GCS 8–12) TBI should have an immediate neurosurgical consult (ideally neurosurgery is part of the trauma response team) followed by a head CT scan without contrast to quickly assess the presence or absence of obvious intracranial trauma. The GCS score can be difficult to interpret in the intubated patient, secondary to prevention of speech and requirement for sedative medications. The GCS measures a patient's ability to understand and follow commands, so it is especially challenging in infants and toddlers and as such has been modified for these age groups. The Children's Hospital of Philadelphia infant coma scale ("Infant Face Scale") provides a useful neurological assessment tool for children under 2 years of age. Serial examinations should be undertaken frequently, with interventions aimed at reducing ICP instituted if there are clinical or radiological signs of herniation syndrome, such as decerebrate or decorticate posturing, anisocoria, or Cushing's triad (bradycardia, hypertension, and Cheyne-Stokes respirations). Patients with moderate TBI should be admitted to an ICU for serial and frequent neurological evaluations, and those with severe TBI should be admitted for neurointensive care monitoring and therapeutic interventions if necessary.

25.4.1.2 Intensive Care Unit Management

Linchpins of neurointensive care management include maintenance of cardiopulmonary parameters, prevention of secondary injury, and optimizing the milieu for potential neurological recovery. Maintenance of adequate oxygenation, targeted ventilation, and blood pressure are paramount. This is facilitated most accurately in severe TBI patients using invasive arterial catheters to measure PaO_2, $PaCO_2$, and continuous blood pressure and central venous catheters to optimize fluid balance and administer vasoactive medications when necessary. $PaCO_2$ should be maintained between 35 and 40 mm Hg in patients unless hyperventilation is being used for refractory intracranial hypertension. PaO_2 should be maintained between 100 and 200 mm Hg in patients unless hyperoxic therapy is being titrated using $CMRO_2$, $SjvO_2$, NIRS, or $PbtO_2$ monitoring. Fluid balance should be carefully recorded, and euvolemia should be the therapeutic goal. Maintenance fluid composition should consist of an isotonic, or perhaps hypertonic, solution, with hypotonic fluids avoided (of note, lactated Ringer's solution is mildly hypotonic). This is because within hours after TBI, the BBB is generally reestablished and the intact BBB is impermeable to sodium and other ions but permits free flow of water across the BBB. Therefore, isotonic or hypertonic fluids would reduce the osmotic pressure for water to transit into the brain (Fig. 25.7). A comparison of hypertonic saline as maintenance fluid for pediatric patients after TBI demonstrated reduced fluid requirement and need for ICP-directed interventions versus lactated Ringer's solution without obvious side effects. Regardless, serum electrolyte levels and osmolality should be checked frequently, and the patient should be monitored for development of SIADH, cerebral salt wasting, and diabetes insipidus. In general, hematocrit should be maintained >30% in severe TBI patients. Transfusion thresholds could potentially be guided by NIRS, $SjvO_2$, and/or $PbtO_2$. Continuous EEG monitoring should be considered for detection of post-traumatic seizures. The pediatric TBI guidelines offer level III evidence for

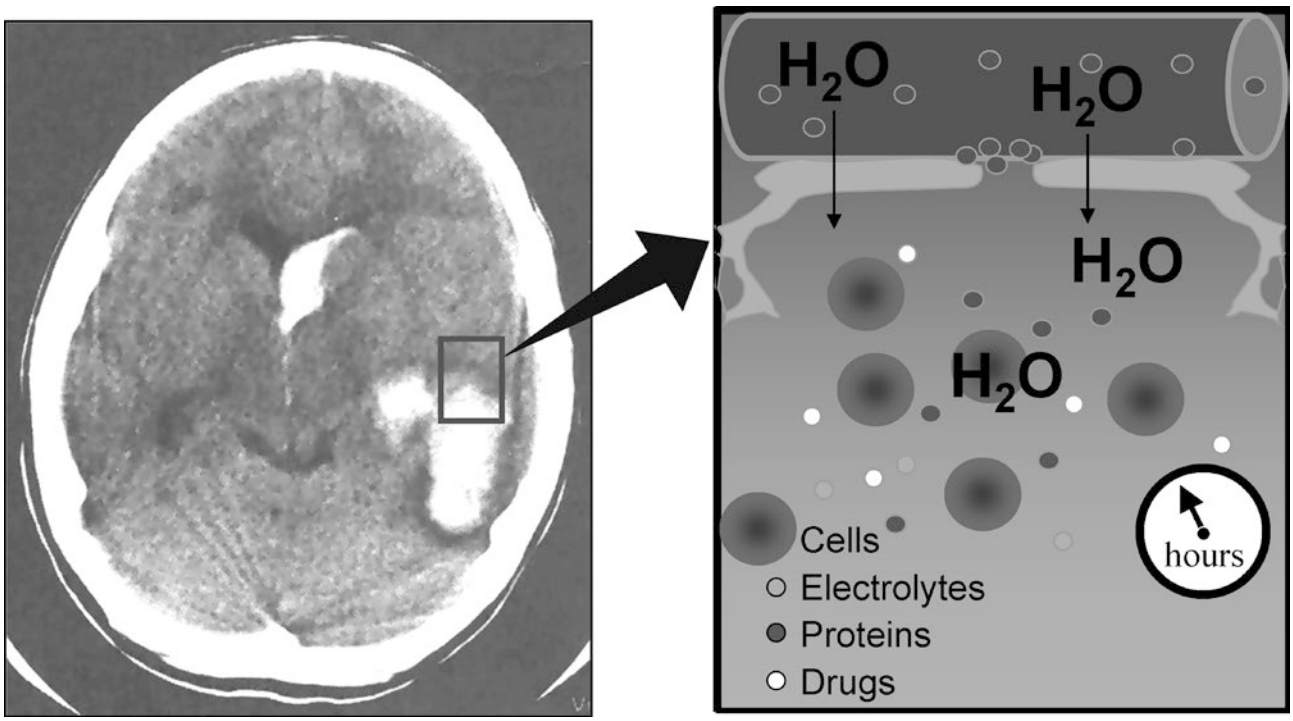


Fig. 25.7 Cerebral edema produced by tissue osmolar load after reestablishment of the blood-brain barrier

consideration of phenytoin for antiseizure prophylaxis. However, more recently levetiracetam has been utilized clinically and in Operation Brain Trauma Therapy (OBTT) has been shown to improve cognitive outcome in rodent TBI models. Important nursing issues include elevating the head of the bed, pulmonary toilet for the prevention of nosocomial pneumonia, and deep venous thrombosis/pressure sore prevention. Related to head of the bed elevation, ICP is minimized when the head is raised, although CBF and CPP were shown to be similar with or without head elevation. It has been suggested that the head of the bed be maintained at 30° in patients at risk for intracranial hypertension. Hyperthermia should be treated immediately, as even small (1–2°) increases in brain temperature exacerbate damage after TBI in experimental models.

Hyperglycemia and hypoglycemia after TBI are associated with worse outcome.

Administration of dextrose in the absence of hypoglycemia is extremely controversial in the first 24–48 h after TBI. Hyperglycemia is associated with worse outcome after TBI in pediatric patients in a "dose-dependent" fashion. Although cause and effect has not been clearly established, all patients in a clinical study presenting with a serum glucose over 300 mg/dL died. Experimental studies show that hyperglycemia at the time of brain insult can exacerbate brain damage, felt to be related to increased lactic acidosis-induced generation of iron-catalyzed free radicals. As such, dextrose is typically avoided in patients with brain injury for approximately 24–48 h unless hypoglycemia and/or ketoacidosis occurs. However, infants, who have immature glycogen stores, may require addition of dextrose to intravenous fluids sooner than older children. An important caveat is that hypoglycemia in brain-injured patients, whether traumatic, ischemic, or excitotoxic in nature, should be avoided at all costs, since hypoglycemia alone can result in catastrophic neurological damage. There is evidence that protocolized glucose control reduces mortality in certain patient populations. In adults with isolated TBI, tight glucose control can reduce mean and maximal ICP, without an effect on CPP, and reduce seizure frequency. In contrast, intensive insulin therapy has the potential to increase lactate/pyruvate ratio, glutamate, and $CMRO_2$ relative to "normal" glucose management, implying detrimental effects of tight glucose control. In pediatric severe TBI, a recent study found that nutrition (enteral or parenteral) initiated less than 72 h after injury was associated with survival and favorable 6- and 12-month outcome. Enteral feeding is preferred; however, parenteral nutrition can be given with careful attention paid to sodium concentration.

Dextrose is typically avoided until 48 h after TBI unless there is hypoglycemia or ketoacidosis, but data are lacking to support this practice.

25.4.1.3 ICP-Directed Therapies

Important for TBI patients is the use of ICP monitoring to enable goal-directed therapy, targeting ICP <20 mm Hg as the "goal." Although level I evidence is lacking, ICP monitoring is often utilized as there is a powerful, albeit not causative, relationship between ICP >20 mm Hg and poor outcome after TBI. There also is a profound relationship between evidence of secondary ischemia during incidents of intracranial hypertension. Clinically elevated ICP is also associated with depressed level of consciousness. Attempts to show benefit with use of ICP monitoring has been mixed. A randomized controlled study of ICP monitoring vs. treatment based on imaging and clinical examination was undertaken in patients 13 years or older in Bolivia and Ecuador. The authors found no difference in functional and cognitive status or 6-month mortality. However, this study has been scrutinized for more intensive hyperosmolar therapy and use of hyperventilation in the imaging-clinical examination group and dissimilarities in care in Latin America vs. the United States. In children, a propensity analysis was performed using two linked national databases and found no evidence of benefit with ICP monitoring on functional survival. The

ability of propensity matching, in this study, to completely adjust for between-group differences (e.g., injury characteristics, therapeutic intensity) has been questioned. Nevertheless, in the present day, ICP remains the primary target for goal-directed therapy in patients with TBI.

Primary or first-tier therapies for severe TBI patients include sedation and paralysis, whose most important function may be facilitation of patient comfort and control of mechanical ventilation. Although there are some theoretical benefits to using sedatives related to reducing cerebral metabolism, there are those who feel that the reduction in blood pressure caused by the sedatives may negate any potential beneficial effects and perhaps may be undesirable. While the use of muscle relaxants without sedation, even in patients in coma, may seem inhumane, certain centers apply this in adult TBI patients and report outcomes that are comparable or better than many trauma centers. Current guidelines support use of sedatives and neuromuscular blockade in children after TBI, however, if for nothing else to minimize wide variations in physiologic variables such as heart rate, blood pressure, $PaCO_2$, PaO_2, glucose, and ICP. Intermittent dosing of osmolar agents such as mannitol or hypertonic saline is also considered first-tier therapies for intracranial hypertension. A single-center study found that hypertonic saline was the most effective intervention with the most favorable hemodynamic profile in pediatric severe TBI patients. However, requirement for multiple doses would suggest refractory intracranial hypertension, warranting use of second-tier therapies.

Treatments for refractory ICP include hypothermia, hypertonic saline infusion, high-dose barbiturates, aggressive hyperventilation, and decompressive craniectomy.

Treatment of refractory intracranial hypertension, defined as an ICP >20 mm Hg sustained for at least several minutes, is often institution dependent and should be tailored to individual patients. Certainly early, non-selective application of ICP-directed therapies to patients with severe TBI with of any of these second-tier therapies (Fig. 25.5) in clinical trials has resulted in either futility, undesirable effects, or even worse neurological outcome, examples including hypothermia, barbiturates, and hyperventilation. Pros and cons for each of these interventions exist and, like anything else in medicine, should be vigilantly applied, monitored, and titrated for each patient. Interventions deserving additional comment include CSF drainage, hyperosmolar therapy, hypothermia, surgical decompression, and barbiturates.

CSF drainage is an effective way of controlling ICP.

Cerebrospinal fluid drainage represents an effective means of reducing ICP. Simply put, if one reduces the CSF volume within the intracranial vault, ICP is also reduced, based on intracranial compliance (Fig. 25.8). Since the intracranial volume is generally fixed, small changes in volume can result in large changes in ICP in patients on the "steep part" of the compliance curve. This concept is referred to as the "Monro-Kellie doctrine" based on observations made around the year 1800. The ability to drain CSF is one advantage of utilizing a ventricular catheter for monitoring ICP, making it both a therapeutic and diagnostic intervention. While there are no controlled trials comparing CSF drainage to other therapies, proponents of CSF drainage report favorable

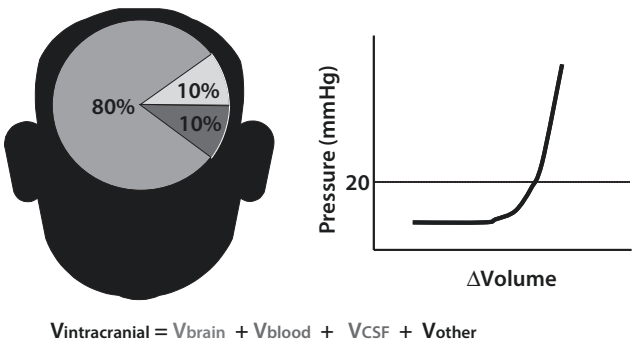


Fig. 25.8 Pressure-volume compliance of the intracranial vault

outcomes in trauma centers utilizing extraventricular catheters therapeutically. Whether to intermittently drain CSF on an "as-needed" basis, versus continuously drain CSF by positioning the drain a certain distance above the midbrain, is also institution dependent.

Hyperosmolar therapy is another effective means of reducing refractory ICP. Mannitol has been the mainstay of osmolar agents for use in TBI, although hypertonic saline (>3% NaCl) is gaining greater acceptance as a primary osmolar agent. Hypertonic saline previously was used mainly for refractory intracranial hypertension, but more recently has been used as the first-line osmolar agent. The rapid reduction in ICP after administration of hyperosmolar agents is due to rheologic effects, not osmotic diuresis. These agents reduce blood viscosity, allowing for reduced blood vessel caliber while maintaining blood flow, represented by Poiseuille's law:

$$Q = \left(\pi \Delta \mathrm{Pr}^4\right) / \left(8 \upsilon l\right)$$

where P = pressure, r = vessel radius, υ = viscosity, and l = vessel length. Epidemiologic studies have shown an independent association between mannitol use and poor outcome in children after TBI. Most studies evaluating the safety and efficacy of hypertonic saline in children after TBI support its use, although studies in adults after TBI in the prehospital setting are less convincing. A head-to-head study examining equimolar doses of mannitol (20%) versus NaCl/dextran (7.5%/6%) suggests that hypertonic saline is more effective in reducing ICP. These factors may result in the replacement of mannitol with hypertonic saline in the future. Most experience after TBI is with the use of 3% NaCl, though higher concentrations, up to 23.4%, are being tested clinically.

Hypothermia reduces ICP but has not been shown to improve outcome after TBI in large multi-center trials.

Hypothermia is another plausible second-tier therapy. Within institutions, hypothermia has been shown to effectively improve neurological outcome after TBI, although multi-center trials did not show efficacy and even a tendency toward harm. The potential beneficial effects of hypothermia after TBI include balancing cerebral metabolism and blood flow, prevention and/or reduction in cerebral edema, and inhibition of inflammation and free radical production. To date, universal application of hypothermia for all patients after TBI cannot be recommended. However, hypothermia may be used for treatment of intracranial hypertension as a second-tier therapy. Complications of hypothermic therapy such as electrolyte abnormalities, dysrhythmias, and coagulation disturbances should be monitored for and corrected. Recent multi-center studies do not support early application of hypothermia in children after TBI. Hyperthermia is associated with poor outcome and may contribute to secondary injury; therefore, antipyretics and active management to prevent hyperthermia using cooling blankets, cold saline infusion, or other temperature management systems may be considered.

Decompressive craniectomy which allows for expansion of edematous brain is an effective way of reducing ICP.

Surgical decompression is another effective means of reducing and/or preventing intracranial hypertension. Decompression via unilateral or bilateral craniectomies changes the architecture of the intracranial vault by increasing intracranial volume and allowing for expansion, throwing the Monro-Kellie doctrine out the window. Both unilateral and bilateral craniectomies have been shown to be effective in reducing ICP in children after TBI. The impact of surgical decompression on outcome after TBI is unclear. A randomized controlled trial of early decompressive craniotomy in adults with diffuse TBI and refractory intracranial pressure resulted in worse 6-month functional outcome in the treatment group compared with the standard care group.

Barbiturates decrease brain metabolic demands but have significant undesirable hemodynamic effects.

Barbiturates have been used for decades to treat refractory intracranial hypertension based on the concept that reducing metabolic demands – putting the brain to sleep – can reduce cell death in regions with compromised sub-

strate and oxygen delivery. While barbiturates certainly reduce cerebral metabolism, this has not yielded improved outcome in patients after TBI. This may be related to undesirable cardiovascular effects of barbiturates, particularly at doses required to achieve burst suppression or "barbiturate coma." If using high-dose barbiturates, monitoring for cardiovascular side effects is essential with immediate correction if/when they occur.

Second-tier therapies for refractory ICP should be tailored to individual patients.

A common theme emerging in terms of choosing second-tier therapies for treatment of TBI is that these therapies should be tailored to individual patients, based on physiologic, radiographic, and perhaps demographic data. When using these therapies, patients should be rigorously monitored not only for beneficial effects (ICP) but also for undesirable effects. Side effects that may counteract or potentially harm patients, such as hypotension, cerebral ischemia, infection, etc., should be immediately corrected and prevented if possible. These therapies should be tailored to individual patients, based on physiologic, radiographic, and perhaps demographic data.

25.4.2 Cardiac Arrest

25.4.2.1 Acute Management

Outcome after cardiac arrest depends upon time to return of spontaneous circulation … seconds matter!

Like treatment of TBI, treatment of the cardiac arrest patient begins with the ABCs of resuscitation. For patients with cardiac arrest, rapid recognition of pulselessness and initiation of CPR improve the likelihood of ROSC, survival, and good neurological outcome. The duration of pulselessness and time required to achieve ROSC are strong predictors of outcome in these patients. In other words, seconds matter and may mean the difference between good and poor outcome. To maximize outcome after out-of-hospital arrests, this mandates a community educated in early recognition of cardiac arrest and institution of CPR with rapid response of healthcare providers. For in-hospital arrests, an organized and efficient response team is necessary.

Important for pediatric cardiac arrest is establishment of an open airway and ventilation and oxygenation. This has diverged from adult CPR guidelines, where restarting the heart and chest compressions are now the first intervention ("CABs"). We feel that it is important to maintain the ABCs in pediatric cardiac arrests, however, related to differences in etiologies between infants and children versus adults. Infants and children are much more likely to have asphyxia as the cause of cardiac arrest, from respiratory failure or shock, as opposed to arrhythmia, which is more prevalent in adults. The initial rhythm in children is more likely to be asystole or bradycardia, with ventricular arrhythmias occurring in perhaps up to 10% of cases of out-of-hospital arrests. The number of ventricular arrhythmia-induced cardiac arrests in children is somewhat higher in in-hospital arrests. That said, reestablishment of circulation should begin immediately after the airway, with effective chest compressions and rapid obtainment of vascular access. Recent findings in observational studies of pediatric in-hospital cardiac arrest resuscitation include (1) mean DBP $\geq$ 25 mm Hg during CPR in infants and $\geq$ 30 mm Hg in children was associated with greater likelihood of survival to hospital discharge and survival with favorable neurological outcome, (2) end-tidal CO_2 measurements during CPR were not associated with survival, (3) chest compression rate between 80 and 100 per minute was associated with more survival to hospital discharge and survival with favorable neurological outcome compared to AHA guideline recommendations (100–120 per minute), and (4) in conflict with findings in adults, time to defibrillation was not associated with survival for children with in-hospital arrest. Current clinical resuscitation research efforts in

pediatrics include (1) improving the quality of CPR – more effective delivery of airway, breathing, and chest compressions by human or device, (2) defining the most effective blood pressure and end-tidal CO_2 targets, and (3) utilizing debriefing procedures following cardiac arrest to improve future CPR outcomes.

Pediatric cardiac arrest is most often caused by asphyxia vs. adult cardiac arrest which is most often caused by cardiac disease.

25.4.2.2 Intensive Care Unit

Currently, ICU care remains entirely supportive for victims of cardiac arrest (Fig. 25.9). While it remains imperative to prevent possible secondary injury from hypotension, hypoxia, seizure, hyperthermia, and hypo-/hyperglycemia, evidence is only beginning to inform unique goal-directed strategies for these patients. Hypotension, hypoxia, and hyperoxia are strongly associated with poor outcome in children after cardiac arrest. The American Heart Association recently published post-resuscitation guidelines for the support of children with post-cardiac arrest syndrome. Recent advances in critical care in general and contemporary neurointensive care monitoring, coupled with recent experimental and clinical studies, rekindle hope that strategies may be developed that may someday improve outcome in infants and children after cardiac

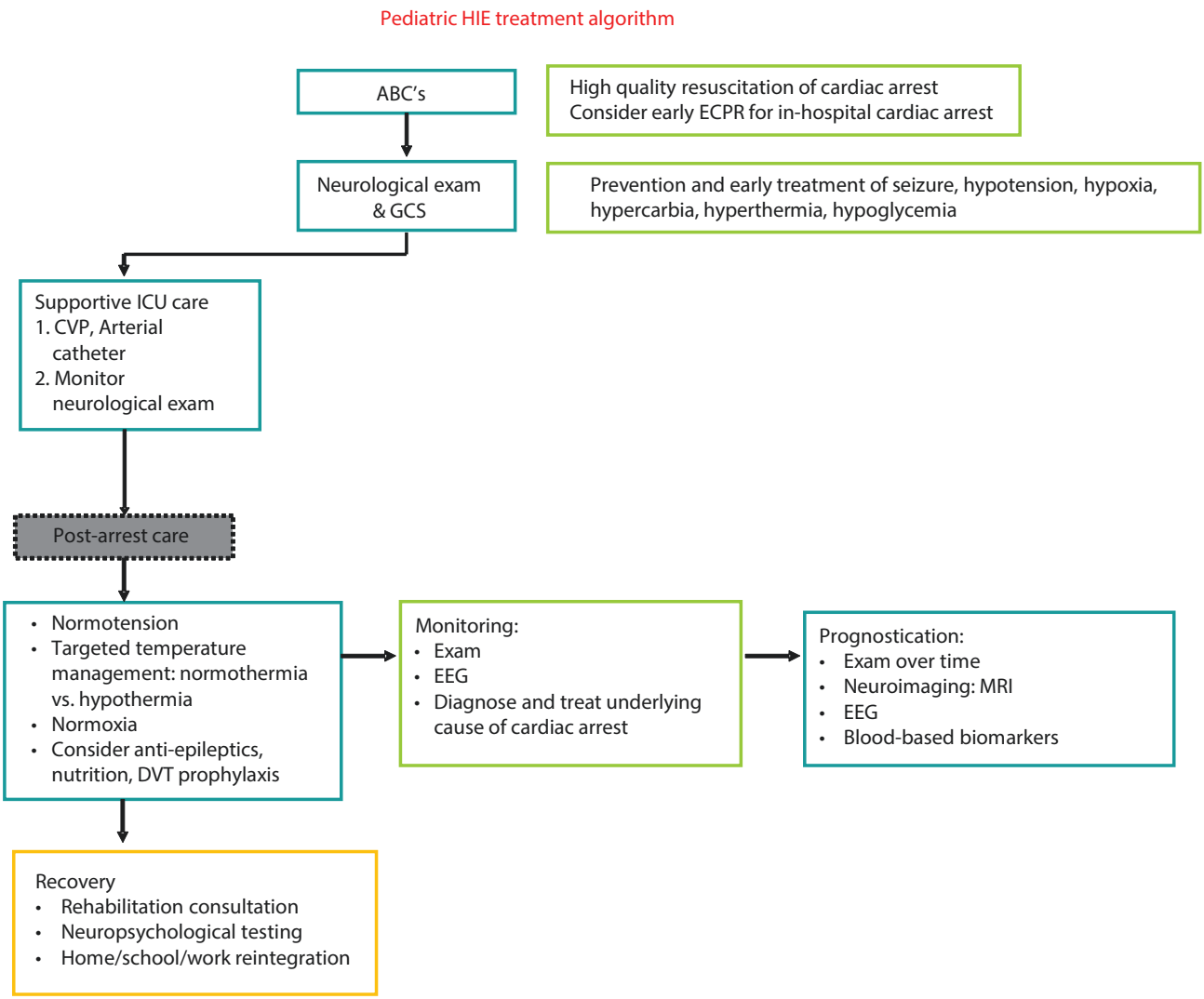


Fig. 25.9 Algorithm for the treatment of cerebral hypoxic-ischemic injury based on the practice and experience at the Children's Hospital of Pittsburgh

arrest. Summary statement - Hypotension is a powerful predictor of poor outcome after cardiac arrest.

The most promising strategy tested in children surviving cardiac arrest resuscitation is the use of induced hypothermia. Improved survival and long-term neurodevelopmental outcomes have been achieved applying 33 °C hypothermia for 72 h in neonates with moderate-severe encephalopathy following birth asphyxia. Promising results when comparing hypothermia to usual care in comatose adults surviving ventricular dysrhythmia-associated cardiac arrest in the early 2000s changed the status quo for post-arrest care until a subsequent trial that used controlled normothermia as a comparison arm demonstrated lack of efficacy of hypothermia. Accordingly, the American Heart Association updated their post-cardiac arrest guidelines to recommend prevention of fever and the use of targeted temperature management (TTM) for all patients. TTM is defined as choosing a target temperature in the range of 32–36 °C and maintaining for 24 h with careful rewarming as a therapy to decrease the incidence of neurological morbidity. In children, the multinational Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) randomized, controlled trials compared hypothermia (33 °C) for 48 h versus controlled normothermia for neuroprotection after in- and out-of-hospital cardiac arrest. The out-of-hospital trial showed no significant difference in the primary outcome, survival with a good functional outcome at 1 year, between the hypothermia group and the normothermia group (20% vs. 12%; relative likelihood, 1.54; 95% confidence interval [CI], 0.86–2.76; $P = 0.14$). The in-hospital trial was discontinued early for futility, finding survival with good neurological outcome at 1 year in the hypothermia group (36% [48 of 133 patients] versus the normothermia group 39% [48 of 124 patients], relative risk, 0.92; 95% CI, 0.67–1.27; $P = 0.63$). Neither trial showed differences in serious adverse events. A single-center pilot randomized controlled trial comparing 24 vs. 72 h hypothermia after pediatric cardiac arrest found favorable brain-based biomarker profiles among children cooled to 72 h versus 24 h, which may warrant further study. Current AHA guidelines for TTM in pediatric cardiac arrest read, "For infants and children remaining comatose after OHCA, it is reasonable either to maintain 5 days of continuous normothermia (36–37.5 °C) or to maintain 2 days of initial continuous hypothermia (32–34 °C) followed by 3 days of continuous normothermia." During hypothermia, attention must be paid to possible adverse events such as electrolyte abnormalities, shivering – which would require administration of muscle relaxants, coagulopathy, or dysrhythmias. Pilot studies using cold saline infusion to achieve target temperatures are feasible, but in the prehospital setting did not lead to improved outcomes and may be associated with adverse effects, thus, not recommended. Hypothermia did not improve survival with good neurological outcome in comatose children who survived initial cardiac arrest but is standard of care for neonates after birth asphyxia.

The American Heart Association lists TTM as a class IIa post-resuscitation treatment recommendation after pediatric cardiac arrest.

Some centers are using extracorporeal membrane oxygenation as a rescue therapy during in-hospital pediatric cardiac arrest (ECPR), especially in patients with cardiac etiologies. ECPR can be implemented during active CPR, although it requires significant resources and highly skilled personnel. ECPR is an effective means of reestablishing cardiac output in patients after cardiac arrest and can be used in combination with TTM since bypass enables maintenance of temperature. Although patients may have had long resuscitation times, good neurological outcome is still possible, with survival rate higher in patients with isolated cardiac disease. Per AHA recommendations, ECPR may be considered for pediatric patients with cardiac diagnoses who have IHCA in settings with existing ECMO protocols, expertise, and equipment (class IIb). Some children with in-hospital cardiac arrest due to non-cardiac cause may still benefit from ECPR, however. Very few data exist to support ECPR for

ECMO may be an effective rescue therapy to obtain ROSC for select patients undergoing active CPR.

out-of-hospital pediatric cardiac arrest. Criteria for ECPR should be thoughtfully considered prior to application of this intensive resource.

Other potential strategies though not trialed in large studies for any population include high-volume continuous veno-venous hemofiltration, which has been shown to improve neurological outcome in a small non-randomized trial in adults after cardiac arrest. Pilot data suggests that a combination of coenzyme Q and mild, induced hypothermia reduces mortality versus hypothermia alone after cardiac arrest. Erythropoietin is under investigation as a co-therapy with hypothermia in neonates with birth asphyxia in a large, randomized controlled trial. Many other pharmacological strategies have been tried, including magnesium with and without diazepam, calcium channel blockers, barbiturates, and steroids – all without success. Translational studies are needed to inform new potential interventions for testing in children with cardiac arrest. Strategies underconsideration include interventionst that target mitochondrial function, oxidative stress, brain edema, and rehabilitation. Personalized interventions using imaging and blood biomarkers may also be helpful to guide patient trial eligibility and response to interventions.

25.5 Epidemiology and Clinical Outcomes

25.5.1 Traumatic Brain Injury

Trauma is the most common cause of death of children worldwide and the #1 killer in the United States.

Pediatric TBI results in 640,000 emergency department visits, 18,000 hospitalizations, and 1500 deaths in the United States annually. In children, the mechanisms of injury include falls (53.6%), strikes by or against an object (26.1%), motor vehicle crashes (4.2%), and assault or homicide (1.8%). Trauma is an important cause of death in children throughout the world and the number one killer of children in the United States. Mortality for severe TBI in children is approximately 24%, with studies finding varying effects of age or gender on survival. Survivors of TBI may suffer from physical, psychosocial, and neurocognitive deficits that have a significant impact on quality of life. Disabilities are seen 12 months following injury in 14% of children with mild TBI and 62% of children with moderate to severe TBI. Outcomes after mild, moderate, and severe TBI in children reveal a strong association between injury severity and outcomes across rehabilitation domains. Males have been found to have worse memory and processing speed when assessed months after injury. As noted above, hyperthermia, hypotension, hyperglycemia, and hypoxemia after TBI are associated with poor outcome after TBI. Importantly, adherence to the Pediatric TBI guidelines, first published in 2003 by the Brain Trauma Foundation, and since updated, has been shown to increase discharge survival and improve discharge Glasgow Outcome Scale.

The GCS has been used to predict outcome in pediatric TBI patients, and although clearly associated with outcome, it is not a sensitive instrument. Modifications of the GCS for children have also been used, including the grimace component of a modified pediatric GCS, found to be more reliable than the verbal component in predicting outcome. Others have used the motor component of the GCS, which may be the most reliable and repeatable component in infants and children after TBI, to demonstrate a linear relationship with survival. The predictive ability of GCS has been shown to be enhanced with the addition of the pupillary exam.

Inflicted severe TBI due to child abuse is associated with extremely poor outcome.

In the pediatric population, TBI is predominately due to blunt trauma and is referred to as closed head injury, but penetrating brain injury also occurs. Outcome after penetrating brain injury is generally poorer versus closed head

injury, with a higher mortality; however, good outcomes in survivors are sometimes observed. Children with inflicted TBI from child abuse represent a growing population unique to pediatric TBI and have a very poor prognosis overall. This may be due to several factors including age, a contribution of hypoxic-ischemic injury, repeated insults, and/or delay in seeking medical attention. Mortality rates range from 13% to 36% with high morbidity seen in survivors, with approximately half of them classified as having severe neurological damage.

25.5.2 Cardiac Arrest

Outcomes for infants and children after cardiac arrest remain disappointing. In an observational study of pediatric out-of-hospital cardiac arrest in North America, the age- and sex-adjusted incidence rate was 8.3 per 100,000 person-years (75.3 for infants vs. 3.7 for children and 6.3 for adolescents, per 100,000 person-years). Most (70%) events were unwitnessed and only 50% received bystander CPR. Survival to hospital discharge was 8.3% overall, (3.2% for infants, 9.3% for children, and 12.7% for adolescents). In multivariable logistic regression analysis, infant age group, unwitnessed event, initial rhythm of asystole, and geographic region were associated with lower survival. Just over half of pediatric cardiac arrest patients are male with equal survival rates between genders. The most prevalent etiologies are sudden infant death syndrome and trauma, which have worse outcomes than those with respiratory and submersion etiologies. Patients suffering witnessed cardiac arrest have better outcomes compared with unwitnessed, but prehospital CPR does not necessarily make a difference in survival rate. Out-of-hospital cardiac arrest patients had better survival if the first assessed rhythm was pulseless electrical activity (24%) or ventricular fibrillation (9%), but most had asystole (67%). Three or more doses of epinephrine or resuscitation >30 min were associated with unfavorable neurological outcome in survivors.

Survival rate to hospital discharge is higher and increasing over time without increasing neurological impairments in one study, for inpatient pediatric cardiac arrest patients versus outpatient cardiac arrest patients (~27%), with approximately 65% of patients in the National Registry of Cardiopulmonary Resuscitation recovering to good neurological outcome. It should be noted that the time to first CPR was <1 min on average with these inpatient arrests. Most in-hospital pediatric cardiac arrests occur within an ICU.

Incidence, etiology, and survival rates following in- and out-of-hospital cardiac arrest for children differ.

In a study of cardiac arrests occurring in PICUs, 139 (1.4%) children received CPR for ≥1 min and/or defibrillation. Of these children, 78% attained ROSC, 45% survived to hospital discharge, and 89% of survivors had good neurologic outcomes. Survival was better for cardiac compared with non-cardiac patients (3.4% vs. 0.8%), but survival with favorable neurologic outcome was not different (41% vs. 39%). Patients who have a cardiac arrest in a pediatric ICU have a hospital discharge rates that differ by CPR duration, <15 min, 15–30 min, and > 30 min, and the survival rates were 18.6%, 12.2%, and 5.6%, respectively. Only 2 (5.7%) of 35 patients who had multiple events of cardiac arrest in the ICU survived to discharge. Severity of illness, as measured by the Pediatric Risk of Mortality III score, was found to be a significant predictor of survival.

Survival rates after cardiac arrest in children: 43% in-hospital and 8% out-of-hospital.

25.6 Summary

25

Inpatient rehabilitation can improve neurological function after moderate-severe TBI.

The goal as intensivists is to improve survival and neurological outcome in infants and children after traumatic or hypoxic-ischemic brain injury. Survival outcomes have improved with modern critical care, but care is largely supportive rather than targeted. Once survival is ensured, the goal is to utilize best practices in the ICU through to rehabilitation and re-integration into the home environment and community with the optimal chance for meaningful recovery. Rehabilitation potential for pediatric patients with moderate-severe TBI can result in significant improvements in neurological function. While there is limited information on the effectiveness of rehabilitation in pediatric patients recovering from cardiac arrest, in adults, significant cognitive improvement and decreased dependency in activities of daily living can be achieved. Early, ICU-based rehabilitative consultation assessments may help inform rehabilitation planning in and out of the hospital. Accordingly, much effort is still required not only to improve the quality and consistency of current management but also to make progress in terms of innovative breakthrough treatments that make a real difference in improved functional outcome in this challenging group of pediatric patients and their families.

Review Questions

1. A 12-year-old male is involved in a motor vehicle accident. A brain computerized tomogram (CT) reveals a small subdural hematoma with multiple punctuate hemorrhages scattered throughout the frontal and parietal cortex. On clinical exam, he is intubated and hemodynamically stable. He opens his eyes minimally, but only to a firm sternal rub. He does not focus. Prior to the intubation, he moaned but made no discernible words. His pupils are equal and reactive. Which of the following is the best motor response that should still prompt consideration of placement of an intracranial pressure monitor?
   A. Extension of his lower extremities in response to noxious stimuli
   B. Flexion of his upper extremities in response to noxious stimuli
   C. Moving all extremities spontaneously
   D. Reaching across midline to resist a noxious stimulus
   E. Withdrawing from a noxious stimulus

2. A 5-year-old girl was involved in a motor vehicle collision where she sustained injury to her brain with multiple punctuate hemorrhages visualized on computer axial tomogram. She also incurred blunt trauma to her abdomen and has a markedly distended abdomen. She has developed marked acute respiratory distress syndrome requiring mechanical ventilation. After placement of a central venous catheter (tip in the superior vena cava), right radial arterial catheter, Foley catheter, and intraventricular intracranial pressure monitor, the following data are obtained:
   A. Arterial blood pressure: 115/67 mm Hg (mean 83 mm Hg)
   B. Central venous pressure: 12 mm Hg
   C. Intra-abdominal pressure: 18 mm Hg
   D. Mean airway pressure: 18 cm H_2O
   E. Intracranial pressure: 22 mm Hg

The correct value of her cerebral perfusion pressure is which of the following?

A. 43 mm Hg
B. 61 mm Hg
C. 65 mm Hg
D. 71 mm Hg
E. 93 mm Hg

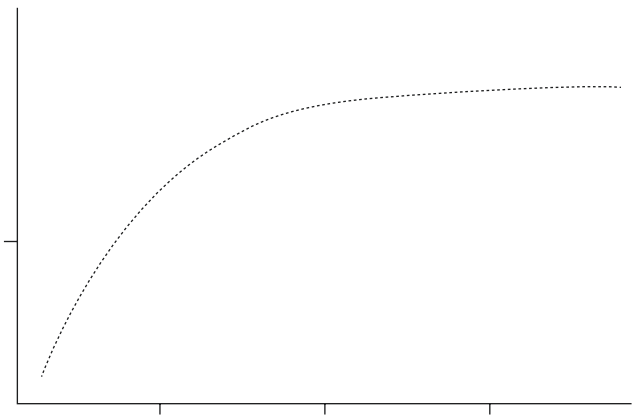
3. Normal cerebral blood flow values (mL/100 g brain/min) are highest at which age of life?

A. Newborns
B. Two years of age
C. Four years of age
D. Adolescence
E. Adulthood

4. The primary value of brain CT immediately after an event associated with significant brain hypoxia-ischemia such as cardiac arrest or drowning is which of the following?

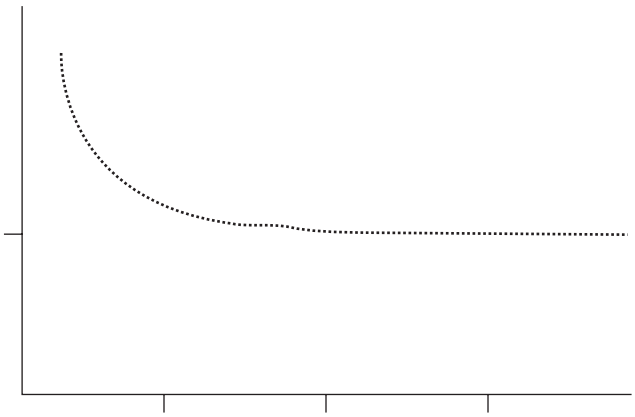
A. A normal initial CT scan of the brain portends a favorable prognosis.
B. Although likely to be normal, it establishes a baseline for comparison with future CT scans.
C. An abnormal initial CT scan indicates a higher probability of an unfavorable neurological outcome.
D. It may be used to assess the possibility of trauma or intracranial hemorrhage as the cause of the cardiac arrest or near-drowning.
E. There is no value to a CT scan of the brain in this setting.

5. The following graph depicts which of the following relationships?



A. The relationship between cerebral blood flow and mean arterial blood pressure
B. The relationship between cerebral blood flow and the initial Glasgow Coma Scale score
C. The relationship between cerebral blood flow and the partial pressure of arterial carbon dioxide
D. The relationship between cerebral blood flow and the partial pressure of arterial oxygen
E. The relationship between cerebral blood volume and intracranial pressure

6. The following graph depicts which of the following relationships?



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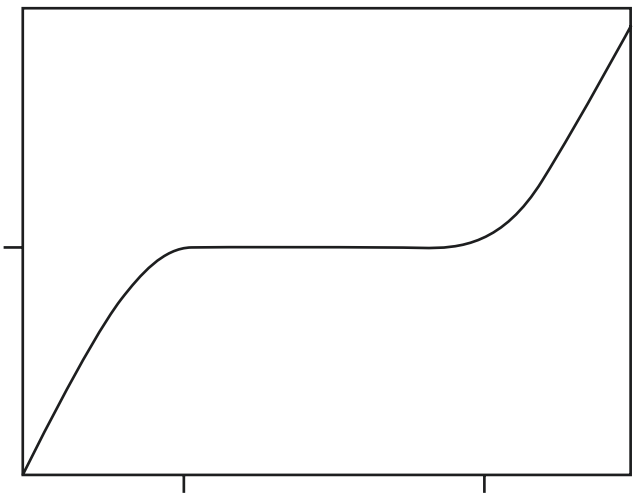
7. The following graph depicts which of the following relationships?



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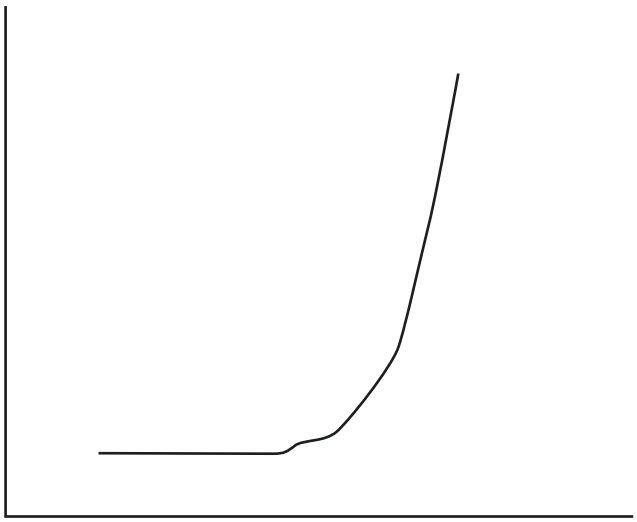
8. The following graph depicts which of the following relationships?



A. The relationship between cerebral blood flow and mean arterial blood pressure
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E. The relationship between intracranial pressure and intracranial volume

9. In the setting of traumatic brain injury, current guidelines support targeting PaO2 between which of the following values?
A. 30 – 45 mm Hg.
B. 45 – 60 mm Hg.
C. 60 – 75 mm Hg.
D. 90 – 100 mm Hg.
E. Targets vary based on age.

10. Which of the following statements regarding the maintenance of body temperature following traumatic brain injury is currently recommended?
A. The induction of extreme hyperthermia should be attempted to optimize neurologic recovery (40–42 °C) as first-tier therapy.
B. The induction of extreme hypothermia should be attempted to optimize neurologic recovery (28–31 °C) as first-tier therapy.
C. The induction of moderate hyperthermia should be attempted to optimize neurologic recovery (38.5–39.5 °C) as first-tier therapy.
D. The induction of moderate hypothermia should be attempted to optimize neurologic recovery (32–34 °C) as first-tier therapy.
E. The maintenance of normothermia with particular attention to avoid any elevation of temperature should be attempted to optimize neurologic recovery.

11. Which of the following statements regarding the maintenance of body temperature following return of spontaneous circulation following cardiac arrest is currently recommended?
A. Axillary temperatures are the gold standard location for monitoring temperature following cardiac arrest.

B. The induction of extreme hypothermia should be attempted to optimize neurologic recovery (28–31 °C) as first-tier therapy.
C. There is no indication to monitor temperature following pediatric cardiac arrest.
D. The induction of moderate hypothermia should be attempted to optimize neurologic recovery (32–34 °C) as first-tier therapy for all patients.
E. The maintenance of normothermia with particular attention to avoid any elevation of temperature should be attempted to optimize neurologic recovery.

Answers

1. E
2. B
3. C
4. D
5. C
6. D
7. A
8. E
9. D
10. E
11. E

Suggested Readings

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Neurological Diseases in Pediatric Critical Care

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Contents

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26

Learning Objectives

- Discuss the differential diagnosis of a child presenting with altered mental status.
- Describe a basic strategy for evaluating and treating a pediatric patient who presents with altered mental status including coma.
- Discuss the presentation, diagnostic workup, and treatment for:
  - Acute disseminated encephalomyelitis
  - Autoimmune encephalitis
  - Reversible posterior leukoencephalopathy syndrome.
- Discuss the causes, treatment, and outcome of status epilepticus in children.
- Describe the time-sensitive and phased approach to controlling status epilepticus.
- Discuss the differential diagnosis of neuromuscular weakness in an infant and older child.
- Describe the presentation, diagnostic workup, and treatment of transverse myelitis and acute flaccid myelitis.
- Describe the presentation, diagnostic workup, and treatment of a child with Guillain-Barré syndrome.
- List indications for mechanical ventilation in a child with Guillain-Barré syndrome.

26.1 Introduction

Data from the largest pediatric critical care collaborative demonstrate that up to 15% of pediatric intensive care unit (PICU) admissions are due to nontraumatic neurologic illness. It is essential that pediatric intensivists have a clear understanding of these disorders to rapidly institute specific treatment to optimize outcomes. Nontraumatic neurologic disorders that routinely challenge the pediatric intensivist, such as altered mental status, status epilepticus, disorders of muscular tone and strength, and inflammatory and infectious diseases of the central nervous system, will be considered in this chapter. Optimal care of children with these disorders is best achieved through close collaboration with a pediatric neurologist.

26.2 Altered Mental Status

Consciousness is a state of complete awareness of self and appropriate interaction with the environment, representing the functional connectivity of neural networks that coordinate both cognitive and affective outputs. Acute failure of these networks can result in various representations of altered mentation, ranging from lethargy, obtundation, and stupor to coma. A working understanding of the various presentations of altered consciousness is essential to the approach to investigating causes of altered mental status.

Lethargy represents a minimally depressed level of alertness, with little stimuli required to arouse. *Obtundation* is a moderate degree of depressed level of alertness with reduced interest and interaction with the environment, where there is generally a slow response to stimuli. *Stupor* is a severe depression in the level of alertness with almost no spontaneous interaction with surroundings. Stupor generally requires vigorous stimulation for brief, simple responses. Typically, it is more important to describe the patient at baseline with additional description of the response to various stimuli, as opposed to simply labeling a disposition. For example, describing a patient as "in bed sleeping, does not arouse spontaneously, but arouses easily to verbal stimuli and appro-

priately responds to examiner," instead of "lethargic," gives subsequent examiners a far better point of reference for comparison.

Coma is "a profound unconscious state from which one cannot be roused." The brain maintains consciousness through a complex and not well-understood interplay between the cerebral cortex and structures within the brainstem. Brainstem structures, called the reticular activating system (RAS), located in the medulla and pons, send signals to the cortex to regulate wakefulness. Small injuries to these areas, and large injuries to the cortex or systemic diseases that affect either structure, can result in the deep disturbance of consciousness that results in the comatose state.

Coma is "a profound unconscious state from which one cannot be roused." The brain maintains consciousness through a complex, and largely not understood, interplay between the cerebral cortex and structures within the brainstem. Brainstem structures, called the reticular activating system (RAS), located in the medulla and pons send signals to the cortex to regulate wakefulness.

Virtually all critical illnesses can eventually lead to coma if a child's condition continues to deteriorate. Metabolic disturbances and compromised oxygen delivery to the brain occur in a variety of critical illnesses that are not primarily neurologic. We will discuss the differential diagnosis of coma as a presenting symptom in primary and secondary neurologic diseases. The differential diagnoses should be considered based on the child's age. A systematic approach to altered mental status (AMS) including stabilization, diagnostic and confirmatory testing, and specific therapies will be outlined.

The causes of coma can be divided into four categories: (1) infectious/inflammatory; (2) vascular; (3) metabolic/toxic; and (4) structural.

26.2.1 Infectious Causes of Altered Mental Status

Primary infections within the central nervous system (CNS) and systemic inflammatory conditions are common causes of AMS in children of all ages. Several pathophysiological mechanisms are believed to be responsible. The release of inflammatory mediators within the brain or meninges may result in cellular dysfunction or cellular death, and this process can eventually lead to decreased consciousness. Similarly, mediators may be released outside the CNS, such as with sepsis or other inflammatory syndromes, and these factors can result in detrimental effects within the CNS. Space-occupying inflammatory lesions, such as brain abscesses or granulomas, can displace and disrupt normal brain tissue as they grow. These lesions may also lead to increased intracranial pressure and disturbance of cerebrovascular hemodynamics, with resultant compromise of perfusion to the brain. Inflammation of cerebral vessels from collagen vascular diseases can lead to alterations in blood flow, eventually leading to coma secondary to inadequate substrate delivery.

Primary infections within the central nervous system and systemic inflammatory conditions are common causes of AMS in children of all ages.

Infectious conditions that must be considered in the child with AMS include meningitis, encephalitis, and brain abscess. These conditions are discussed in more depth in ► Chap. 35. Although these conditions can affect children at any age, the risks vary slightly by age. Infants are most susceptible due to the functional immaturity of their immune system (both humoral and cellular components of immunity are naive compared to older children) and newborn exposure to maternal pathogens during birth. Meningitis due to *Group B streptococcus*, gram-negative bacteria, and encephalitis due to herpes simplex virus type 1 should be considered in this age group.

Viral causes of meningitis and encephalitis predominate in older children and adolescents (e.g., enteroviruses, herpes simplex virus type 2); however, serious bacterial CNS infections from *Neisseria meningitidis* and *Streptococcus pneumoniae* also pose a significant risk. Encephalitis from insect-borne pathogens (e.g., arboviruses, *Borrelia burgdorferi*) can also occur in older children. In low-resource countries, malaria is a common cause of meningoencephalitis leading to AMS.

26.2.2 Inflammatory Causes of Altered Mental Status

26.2.2.1 Acute Disseminated Encephalomyelitis (ADEM)

Acute disseminated encephalomyelitis (ADEM) is an inflammatory condition that often follows an infection or vaccination. Despite many synonyms, including acute demyelinating encephalomyelitis, postinfectious encephalomyelitis, and postinfectious multifocal encephalomyelitis, the consistent pathophysiologic feature appears to be immune-related damage to white matter within the brain and spinal cord. Children are more commonly affected than adults, but there does not appear to be a defined age of maximum risk. The clinical presentation of ADEM is dependent upon the primary affected brain region, but multifocal neurological deficits are almost always present. Pyramidal signs (e.g., spasticity, weakness, slowed rapid alternating movements, hyperreflexia, and a Babinski sign), hemiplegia, ataxia, and cranial nerve lesions all occur commonly. However, in severe cases, coma and global cerebral dysfunction can also be observed.

Diagnosis is often made by establishing a history of previous infection (up to 91% of cases have such a history), clinical examination consistent with encephalopathy, and multifocal neurologic abnormalities. Magnetic resonance imaging (MRI) is essential in establishing the diagnosis. On MRI, T2-weighted and fluid-attenuated inversion recovery (FLAIR) images demonstrate patchy areas of increased signal intensity in multiple areas of the white matter (Fig. 26.1a). Brainstem and spinal cord abnormalities on MRI are commonly seen in ADEM. Spinal cord abnormalities appear as longitudinal rather than segmental lesions. Rarely, hemorrhagic demyelinating lesions can be seen on MRI in the setting of hyperacute ADEM.

On MRI with ADEM, T2-weighted and fluid-attenuated inversion recovery images demonstrate patchy areas of increased signal intensity in multiple areas of the white matter.

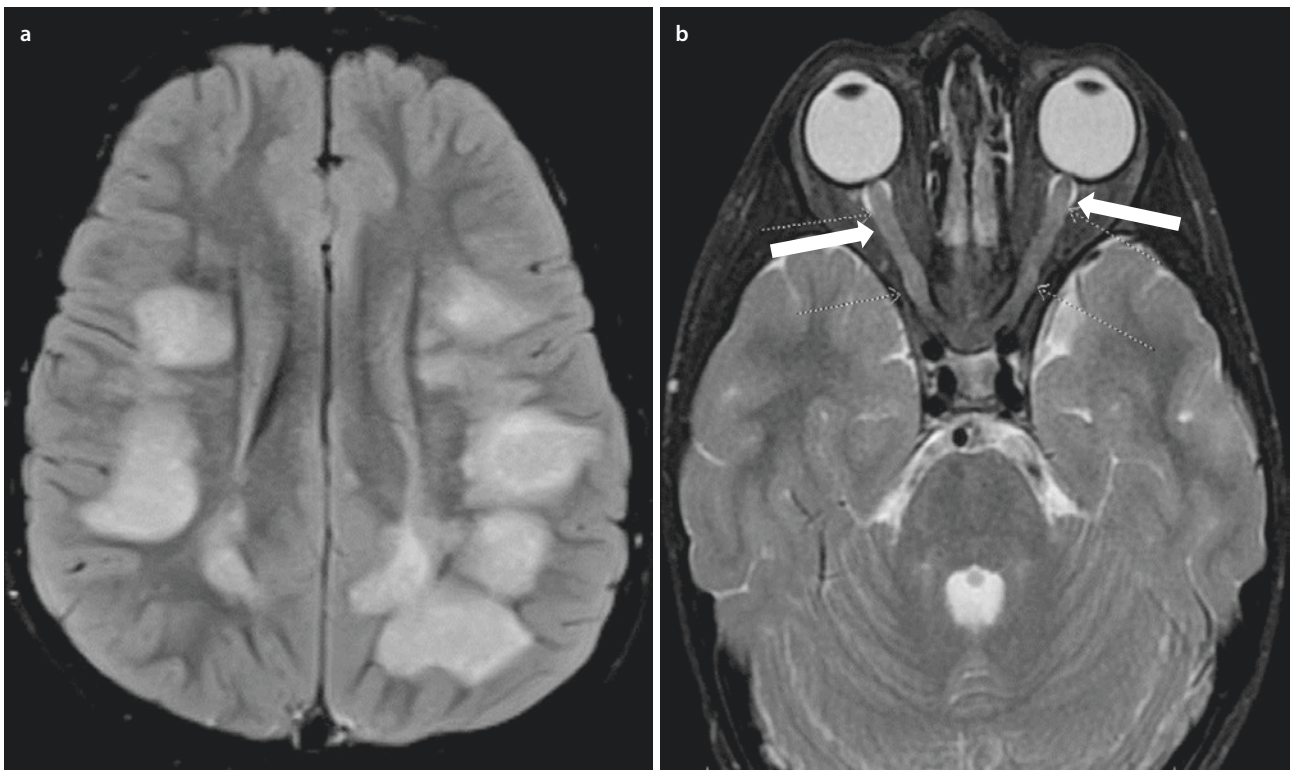

Fig. 26.1 **a** A 7-year-old with ADEM with multiple subcortical lesions demonstrated on T2 flair. (*Courtesy of Dr. Gino Mongelluzzo, MD*). **b** A 4-year-old with recovering ADEM and subsequent optic neuritis (arrows) within 2 weeks of presentation, axial view

CSF examination reveals a mild pleocytosis with lymphocyte predominance and uniformly negative culture results. Serum-based analysis for anti-myelin oligodendrocyte glycoprotein (anti-MOG) IgG autoantibody and the aquaporin-4 (AQP4) IgG autoantibody has become a critical part of evaluation in ADEM. During the first episode of ADEM, MOG antibodies are positive in high titers with return to undetectable levels after recovery. However, persistent MOG antibodies are considered prognostic for incomplete recovery of ADEM, possible relapsing course, or risk for development of other neuroinflammatory diseases, such as optic neuritis. Evidence of MOG antibodies can both impact the acute management and affect clinical decision-making for more chronic therapy. It is important to note that MOG antibodies are not specific for ADEM and can be present in other neuroinflammatory conditions. The anti-AQP4 IgG antibody is a specific biomarker for neuromyelitis optica spectrum disorder, which should be considered if optic neuritis is present (◘ Fig. 26.1b).

There is currently no consensus guideline for the treatment of ADEM, but uncontrolled case series using high-dose glucocorticoids, intravenous immunoglobulin (IVIG), and plasma exchange have been reported in the literature. Traditionally, initial treatment of ADEM has been methylprednisolone 10–30 mg/kg day (1 g max) for 3–5 days. Children who have a poor response to intravenous methylprednisolone should have either IVIG or plasma exchange as a second-tier treatment.

Most children with ADEM recover to baseline, slowly improving over 4–6 weeks. However, 20–30% may have persistent motor or cognitive impairments. In patients with MOG antibodies, there are considerations for continued immunotherapy until levels are undetectable.

26.2.2.2 Autoimmune Encephalitis (AE)

Autoimmune encephalitis (AE) is a non-infectious, immune-mediated inflammation of the brain often involving primarily the gray matter with or without additional involvement of the white matter, meninges (meningoencephalitis), or spinal cord (encephalomyelitis). Antibodies targeting neuronal surface or synaptic antigens may occur as part of a paraneoplastic process, result from a postinfectious etiology or occur idiopathically. A paraneoplastic etiology is more common in adults with AE than in children. Paraneoplastic conditions are commonly related to antibodies against intracellular onconeuronal antigens, suggestive of a T-cell-mediated immune response against the neoplasm with secondary response against the central (and peripheral) nervous system (CNS). Commonly identified autoantibodies in children include those targeting the N-methyl-D-aspartate receptor (NMDAR), the voltage-gated potassium channel (VGKC), glutamic acid decarboxylase (GAD65), and MOG. Autoantibodies to NMDAR have been associated with reactivation of Epstein-Barr virus infection. An autoimmune response to group A beta hemolytic streptococcus infection is thought to mediate pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and its later, broader iteration, pediatric acute-onset neuropsychiatric syndrome (PANS). Most of these children with acute-onset neuropsychiatric symptoms, such as obsessive-compulsive disorder, will not require critical care; it illustrates the growing awareness of postinfectious complications causing neurologic syndromes.

Serum and CSF autoantibody and paraneoplastic panels should be obtained when considering the diagnosis of AE. Identification of these autoantibodies strongly supports the diagnosis of AE, but it is not uncommon for seronegative AE to occur. A diagnosis of seronegative AE is based on clinical features consistent with AE (◘ Table 26.1) in combination with a positive

Table 26.1 Clinical signs and symptoms suggestive of autoimmune encephalitis (AE)

AE involvement	Clinical sign/symptom
Cognitive	Altered mental status, abrupt deterioration in cognitive performance
Psychiatric	Personality changes, mania, catatonia, psychosis
Epileptic	New-onset seizure disorder (focal), status epilepticus
Movement	Dystonia, dyskinesia, chorea, parkinsonism
Ataxic	Impaired coordination
Autonomic	Brady–/tachycardia, hyper–/hypothermia, bowel/bladder dysfunction
Craniobulbar	Ophthalmoplegia, dysphagia, facial weakness
Sleep	Parasomnias, hypersomnia, insomnia, sleep-disordered breathing
Meningeal	Meningeal enhancement, neck stiffness
Optic/spinal	Optic neuritis, transverse myelitis
Neuromuscular	Neuropathy, myotonia

response to immunotherapy. If AE is suspected and the child is functionally impaired, empiric therapy with immunomodulation should be initiated while awaiting the results of immunologic testing, as early treatment has been correlated with improved outcomes.

In the absence of consensus data, treatment for AE resembles the immunomodulatory approach used in ADEM. Initial treatment with intravenous methylprednisolone may be followed with IVIG or plasma exchange if there is no improvement. Although some centers may administer IVIG after plasma exchange, there are no data demonstrating that this approach improves outcome. Most centers utilize either rituximab (monoclonal antibody that targets CD20, a specific B-cell surface antigen) or cyclophosphamide in refractory cases.

26.2.3 Vascular Causes of Altered Mental Status

A wide variety of vascular insults can lead to altered mental status, including coma, in children.

A wide variety of nontraumatic vascular insults can lead to altered mental status in children including (i) arterial or diffuse microvascular thrombosis, (ii) vascular rupture (from arteriovenous malformations or aneurysms), (iii) venous thrombosis, and (iv) hypoxia/ischemia after cardiac arrest.

Perinatal strokes are recognized more frequently with improved neurological imaging. These strokes are intrauterine events often associated with perinatal infections. Strokes can occur in toddlers and older children with predisposing conditions, such as sickle cell disease and Moyamoya disease. Between 60% and 90% of children with sickle cell disease have abnormal narrowing of major cerebral vessels detectable by transcranial Doppler imaging (increased flow velocity due to vessel stenosis), angiography, or magnetic resonance angiography. A child with sickle cell anemia is 250 times more likely than other children to experience an acute ischemic stroke in childhood due to chronic cerebrovascular obstruction. Transfusion therapy for children with sickle cell anemia transitioning to hydroxyurea therapy and monitoring for abnormal transcranial Doppler blood flow velocities may prevent or significantly delay the onset of acute ischemic stroke.

Moyamoya disease is a vasculopathy characterized by stenosis or occlusion of the carotid arteries or more distal arteries that feed into the circle of Willis. "Moyamoya" is a Japanese word meaning puff of smoke referring to the smoky angiographic appearance of the numerous collateral vessels that develop to compensate for the progressive arterial occlusion. The etiology of Moyamoya disease is unknown, but recent evidence suggests that the *RNF213* gene on chromosome 17q25.3 is an important susceptibility factor for Moyamoya disease especially in East Asian populations. Associated conditions include sickle cell anemia, Down syndrome, Graves' disease, Alagille syndrome, neurofibromatosis type 1, coarctation of the aorta, and renal artery stenosis.

Moyamoya disease is a known cause of childhood stroke (Fig. 26.2). Clinical features of Moyamoya disease are identical to those of early-onset stroke, with a history of episodes of transient ischemia often preceding the presentation resulting from permanent ischemic changes if the transient ischemic events are not recognized. These symptoms arise because the vast networks of collateral arterioles and capillaries that develop in response to the progressive proximal stenosis of the internal carotid artery steal blood flow from distal regions of the brain.

Clinical features of Moyamoya disease are identical to those of early-onset stroke, with occasional episodes of transient ischemia ultimately presenting with permanent ischemic changes if not recognized.

Definitive diagnosis can be made by MR or computerized tomography (CT) angiography. The use of conventional cerebral angiography has declined due to improved MRI techniques, particularly diffusion and perfusion magnetic resonance scanning.

Surgical treatment for Moyamoya disease includes direct and indirect revascularization techniques designed to reduce the risk of ischemia by improving the cerebral circulation. Superficial temporal artery to middle cerebral artery (MCA) bypass and middle meningeal artery to MCA bypass are the most common direct techniques. Direct methods may be difficult to perform in small children due to vessel size. Indirect revascularization serves to promote the

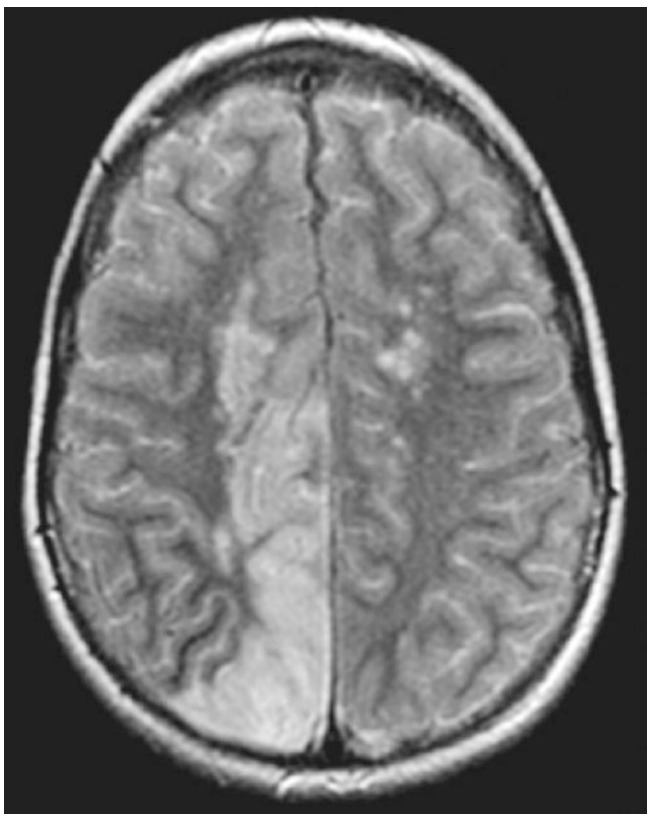

Fig. 26.2 A 6-year-old female presenting with seizure and altered consciousness. T2 MRI demonstrates large infarction in the distal right anterior cerebral artery distribution. In addition, punctate infarcts are seen in the para midline left frontal lobe. Subsequent MRA and angiography revealed bilateral stenosis of the terminal internal carotid arteries with right worse than left consistent with the diagnosis of Moyamoya disease

development of new vascular connections to reduce the risk of the collateral steal phenomenon and ischemia. In general, indirect revascularization requires less operative time and has lower complication rates than direct revascularization. Indirect techniques include re-supplying cerebral blood flow from extracerebral sources by EDAS (encephaloduroarteriosynangiosis) via bypass grafting of vessels within the scalp to the dura mater above the affected cortex.

Sudden onset of AMS, including coma, can be the presenting symptom of either bleeding from malformed arterial-venous connections or rupture of aneurysms in children of all ages.

Hypertensive syndromes and illicit drug use (cocaine, methamphetamine) can lead to stroke in the adolescent and must be considered. Malformed arterial-venous connections or rupture of aneurysms can lead to AMS. In general, rupture of these structures leads to release of blood elements into the parenchyma surrounding the vessel and ischemia in downstream vascular beds. Sudden onset of AMS can be the presenting symptom of either of these entities, and children of all ages are at risk.

Venous thromboses can cause AMS by impeding blood flow from critical regions of the brain. In infants, illnesses causing severe dehydration can lead to thrombosis of the large sinuses within the brain, leading to AMS, including coma. Intracerebral venous thromboses can rarely occur in older children with disorders of the coagulation system. The need to rapidly recognize occult nonaccidental traumatic brain injury as a cause of AMS in infants is an unfortunate reality. In the first months of life, inflicted trauma to the infant's brain can cause a wide variety of injuries leading to AMS including diffuse axonal injury, subdural hematoma, and subarachnoid hemorrhage.

Lastly, although relatively rare in young children, collagen vascular diseases can lead to altered consciousness and must be considered in older children. Systemic lupus erythematosus (SLE) is the most common collagen vascular disease in childhood causing CNS symptoms including coma. An adolescent with altered mental status associated with other symptoms (e.g., rash, joint involvement, fever) should create suspicion for a vasculitis-induced condition. CNS complications of SLE include seizures, ataxia, chorea, stroke, and hemorrhage.

26.2.3.1 Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy is a syndrome that is marked by progressive mental status changes, headache, visual disturbances, seizures, and characteristic neuroimaging findings often associated with acute hypertension.

Reversible posterior leukoencephalopathy syndrome (RPLS) is a rare syndrome that was first described in 1996. The term *RPLS* is synonymous with the frequently used term, *posterior reversible encephalopathy syndrome* (PRES). Clinical presenting features of RPLS include AMS, headache, visual disturbances, and seizures. CT and MRI reveal cerebral edema without infarction usually seen in the posterior regions of the brain, frequently involving the parietal and occipital lobes (◘ Fig. 26.3).

Although not completely understood, the pathogenesis of RPLS is likely due to the interplay of two mechanisms: dysfunctional cerebral autoregulation coupled with a compromised cerebral endothelial barrier that creates areas of focal vasogenic edema. The cause of selective involvement of the posterior circulation is unclear but may be due to relatively sparse sympathetic innervation of the vertebrobasilar system.

Clinically, patients often have significant underlying disease that becomes complicated by progressive mental status changes frequently heralded by headache. Patients may become agitated or somnolent and often progress to stupor or frank coma in severe cases. Seizures may be a presenting feature and are often multiple and generalized. Visual changes are very common and include

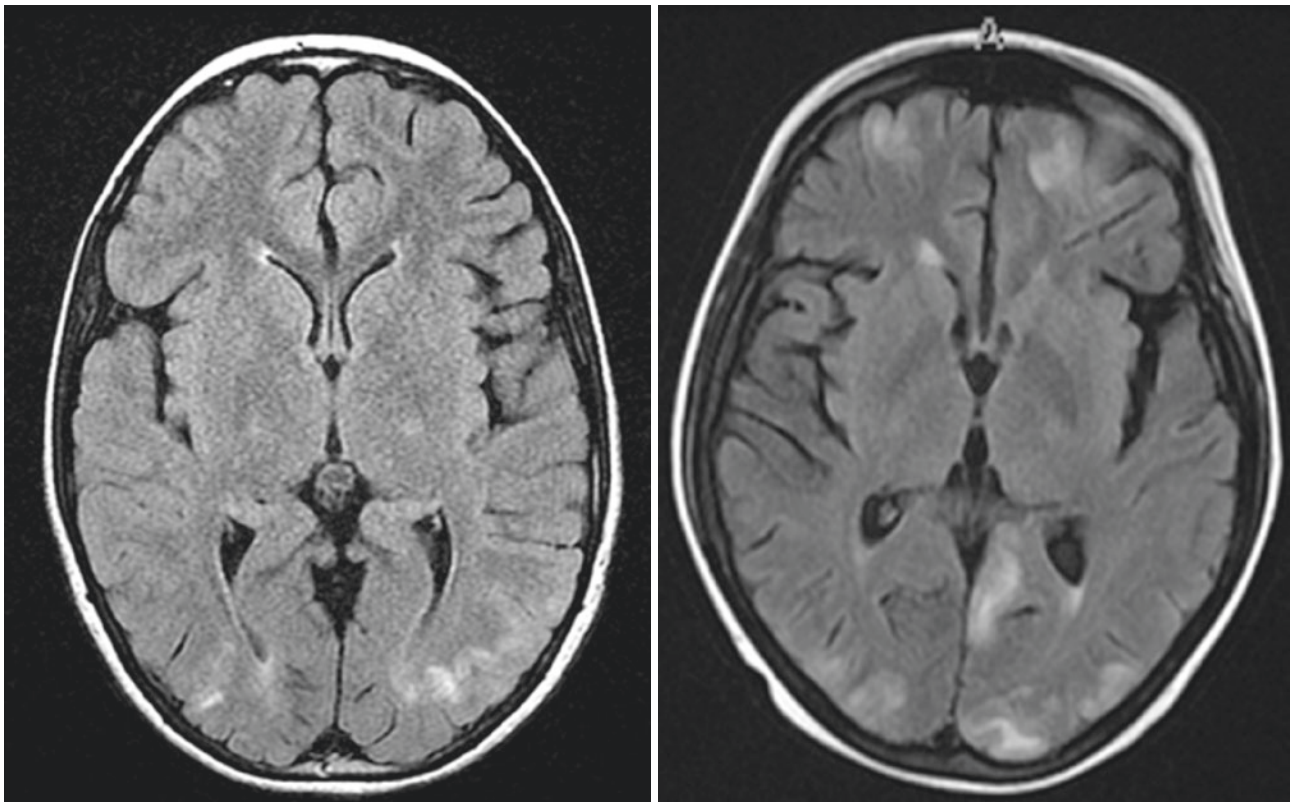

Fig. 26.3 Two patients with clinical and neuroimaging findings consistent with RPLS. Patient 1 (*left*) presented with somnolence, mild hypertension, and a generalized seizure following induction chemotherapy for lymphoma. MRI T2 FLAIR revealed bilateral occipital white matter edema. Patient 2 (*right*) presented with severe hypertension and neurologic changes progressing to deep coma. The patient was receiving high-dose steroids for immunosuppression. MRI T2 FLAIR revealed multiple areas of increased signal intensity indicating vasogenic edema involving the cortices of the frontal lobes, along the watershed territory, and the cortices of the temporal, parietal, and occipital lobes bilaterally

hemianopsia, visual neglect, and cortical blindness. Hypertension is frequent but may be mild or even absent. In cases presenting with severe hypertension, the syndrome may be indistinguishable from hypertensive encephalopathy and should be treated as a hypertensive emergency.

Characteristic neuroimaging findings are best seen on T2 flair MRI and include:

- Symmetrical white matter edema in the posterior cerebral hemispheres, particularly the parieto-occipital regions.
- Anterior cortical involvement is rare but can be seen in more severe cases with concomitant posterior findings.
- Involvement of the cerebellum and brainstem is common.
- Abnormalities primarily affect the subcortical white matter, but the cortex and basal ganglia may be involved.
- Frequent resolution of findings on neuroimaging within days to weeks.

Conditions commonly associated with RPLS/PRES include hypertensive encephalopathy, preeclampsia, eclampsia, and the use of immunosuppressive/neurotoxic drugs. Other associated conditions are summarized in ► Box 26.1.

Box 26.1 Conditions and medications associated with the development of reversible posterior leukoencephalopathy syndrome (RPLS)

Conditions

Hypertension
Preeclampsia/eclampsia
Post-transplantation states (solid organ or bone marrow)
Autoimmune diseases (systemic lupus erythematosus)
Electrolyte disorders (hypercalcemia, hypomagnesemia)
Endocrine disorders (primary aldosteronism, pheochromocytoma)
Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
Sepsis
Liver failure
Massive blood transfusion/erythropoietin therapy
Porphyria

Medications

Immunosuppressives (especially calcineurin inhibitors: cyclosporine and tacrolimus)
Immunomodulators (intravenous immunoglobulin (IVIG), bevacizumab)
Antineoplastic (cytarabine, cisplatin)
High-dose steroids

Treatment of PRLS involves control of hypertension, treatment of seizures, and if possible, reducing neurotoxic medications. Once the underlying trigger (e.g., hypertension) is controlled or offending agent is eliminated (e.g., medications), complete reversibility of both clinical signs and imaging lesions is a defining feature of RPLS. Hypertension should be treated in all cases. Malignant hypertension should be treated in the PICU with titratable parenteral agents such as nicardipine or labetalol (see ► Chap. 20). Care should be taken not to overcorrect malignant hypertension. A reduction in the initial blood pressure by 20% over 2 h is an appropriate goal.

Seizures are best treated with blood pressure control and antiseizure medications: benzodiazepines and if needed either levetiracetam or phenytoin. In the setting of eclampsia, treatment involves delivery of the baby. Magnesium should be used to treat acute seizures pending delivery.

26.2.4 Metabolic/Toxic Causes of Altered Mental Status

Newborns are linked to the maternal circulation during *in utero* development, masking disorders of metabolism that can later lead to disturbances in consciousness.

There are numerous metabolic disorders that can cause AMS. Endogenous and exogenous metabolic substances can alter neuronal functioning and decrease consciousness. Abnormal metabolic compounds can be formed from defective enzymatic action, leading to CNS abnormalities. Additionally, abnormal substrate availability or substrate delivery can lead to AMS change, including coma. Specific metabolic causes include hyper-/hyponatremia, hyper-/hypoglycemia, hypercalcemia, hyper-/ hypothyroidism, hypoxemia, hypercapnea, hepatic encephalopathy, and uremic encephalopathy. Inborn errors of metabolism may lead to hyperammonemia or the accumulation of organic acids that may reduce consciousness.

Newborns are linked to the maternal circulation during *in utero* development, masking disorders of metabolism that can later lead to disturbances in consciousness. Inborn errors in amino acid, lipid, or carbohydrate metabolism can lead to acid-base imbalance, hypoglycemia, or hyperammonemia in infants.

There are numerous potential medications (e.g., opioids, sedatives, and clonidine) and toxins that can alter mental status. The latter include carbon monoxide, lead poisoning, and accidental or intentional overdose of any drug that depresses CNS activity such as anticonvulsants, anxiolytics, and antipsychotic agents. Acetaminophen overdoses can result in acute hepatic failure with hepatic encephalopathy. Exogenous CNS toxins should be considered in toddlers who are at risk for accidental poisonings or purposeful poisoning as part of the Munchausen syndrome by proxy. In addition, toddlers may attach a clonidine or fentanyl patch that was disposed by an adult in the household resulting in acute depression in consciousness sometimes leading to respiratory failure. Adolescents may intentionally ingest toxins during suicide attempts or ingest drugs of abuse which can cause profound AMS.

Several mitochondrial disorders may present in childhood with acute onset of seizures or stroke-like symptoms often between 2 and 10 years of age after initially normal development. Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) result from one of the several mutations in mitochondrial DNA, indicating that the disorder is inherited from the child's mother since sperm lack mitochondria. Early symptoms may include muscle weakness and pain, recurrent headaches, loss of appetite, vomiting, and seizures. Acute episodes are often, but not always, accompanied by lactic acidosis. MR imaging is helpful to demonstrate that the stroke-like imaging seen on CT scan is vasogenic rather than demonstrating reduced blood flow.

26.2.5 Structural Causes of Altered Mental Status

The brain is formed from complex invaginations of epithelial tissue, ultimately leading to the cerebral cortices, midbrain, and all the structures needed for wakefulness. When the genetic programming that outlines these processes is interrupted during embryogenesis, congenital brain malformations occur, and consciousness may not be possible. In extreme cases, such as anencephaly, infants never achieve consciousness because the cortex and brain never completely formed. In less extreme examples, such as neuronal migration disorders, abnormal nests of neurons may impair consciousness permanently or may predispose to seizures.

Acquired structural causes of AMS in older children include hydrocephalus and masses (e.g., tumors, cysts, arteriovenous malformations) which can impair consciousness. If the mass is located within the RAS, consciousness can be impaired by direct disruption of the connections between the cortex and the midbrain. If the mass is located near the RAS, localized swelling can disrupt axonal or glial function in the region and lead to disruptions in consciousness. Finally, masses distant from the RAS can lead to cerebral herniation as intracerebral compliance is impaired.

26.2.6 Evaluation of the Child with Altered Mental Status

With a host of potential causes in mind, the evaluation of a child with acute AMS, including coma, needs to be broad enough to make the diagnosis while being targeted enough to avoid unnecessary testing. Careful consideration of the history of the present illness and concurrent illnesses and consideration of the child's age should guide the initial workup. Physical examination can provide clues to prioritize the possible causes, though most children with AMS including coma, do not have distinguishing physical findings. Any infant or toddler who presents with unexplained AMS should have a fundoscopic exam to look for evidence of nonaccidental trauma. Conclusive diagnosis of AMS

usually requires laboratory testing or neuroimaging. Screening laboratory tests for glucose and electrolytes, renal and liver function, assessment of acid-base balance, and evidence of infection are indicated. When metabolic disorders are suspected, particularly in neonates, serum ammonia, amino acids, and urine organic acids should be determined. Serum and urine toxicological screening is required whenever drug or toxin ingestion is suspected. Examination of cerebrospinal fluid is essential for the diagnoses of meningitis, encephalitis, and certain metabolic disorders and should be performed when clinically indicated and safe. In some cases, genetic evaluation may be helpful, but cost and delay in receiving the test result are limitations. CT scan of the brain affords rapid detection of structural or traumatic abnormalities and should be used if there is acute decompensation. However, MRI scanning may detect more subtle brain abnormalities and is more likely to be revealing.

26.3 Status Epilepticus

Status epilepticus (SE) is generally categorized as either convulsive (CSE) or nonconvulsive (NCSE). CSE describes a child with obvious motor convulsions for the duration of the observation period, while children with NCSE exhibit a wide variety of neurological signs (coma, confusion, somnolence, delusions, hallucinations, aphasia) which make diagnosis and determination of duration more difficult. It should be noted that children with CSE may develop less obvious motor signs during the progression of the seizure activity and this should not delay or diminish aggressive treatment to mitigate these events.

Of children with CSE, one-third occur at the initial presentation of childhood epilepsy. Another one-third were already diagnosed with childhood epilepsy, and the remaining one-third suffered an acute insult resulting in CSE. Over a period of 5 years, children with epilepsy have a 20% chance of having at least 1 episode of CSE. Withdrawal or inadequate serum level of prescribed anticonvulsant(s) often related to issue with medication adherence is a leading cause of CSE. In children with a low seizure threshold, an intercurrent infection, fever, or sleep deprivation can precipitate CSE. In children with CSE in the absence of a prior diagnosis of epilepsy, metabolic disorders (e.g., hypocalcemia, hypoglycemia, and hypo- or hypernatremia), meningoencephalitis, spontaneous hemorrhages, and mass lesions need to be excluded. In contrast, NCSE occurs almost exclusively in children with epilepsy or following a severe hypoxic-ischemic insult such as near drowning or cardiac arrest.

The pathophysiology of brain injury during SE is complex and only partly understood. The instigating seizure nidus may come from neurons damaged during development or loss of inhibitory inputs that are required to maintain electrical homeostasis. As the seizure progresses and more brain area becomes involved, overall cerebral metabolic rate is increased, and a concomitant increase in cerebral blood flow occurs. Eventually, the continuous ictal activity overcomes compensatory mechanisms to increase cerebral blood flow and neuronal glucose and oxygen demand exceeds supply. In these instances, progressive hypoxic damage to neurons can develop and may lead to irreversible damage. Other mechanisms, such as excessive excitotoxicity with reduced activity in inhibitory pathways, are undoubtedly involved in this process as well.

The 2012 Neurocritical Care Society's Guideline on the Evaluation and Management of Status Epilepticus stressed the need for a time-based approach to the control of SE. The guideline defined SE as 5 min of continuous clinical or electrographic seizure activity, and it established the goal of achieving definitive control of status epilepticus within 60 min of onset. The urgent need to control SE was further endorsed by the 2016 American Epilepsy Society's Guideline for Status Epilepticus Management which provided a time-sensitive and phased approach to controlling SE (Fig. 26.4). The guideline was

endorsed by the Epilepsy Foundation, Child Neurology Society, Association of Child Neurology Nurses, American College of Emergency Physicians, and American Association of Neuroscience Nurses.

The guideline follows the 5-min definition and provides a treatment algorithm that is separated into stabilization and three subsequent phases of treatment:

- *Stabilization phase* (0–5 min of seizure activity): Use standard assessments of airway, breathing, and circulation. Obtain monitoring, intravenous (IV) access, and bedside glucose determination. Perform serum electrolytes and other diagnostic studies as indicated.
- *Initial therapy phase* (5–20 min of seizure activity): Utilize benzodiazepines for seizure termination (e.g., intramuscular (IM), IV lorazepam, or IV diazepam).
- *Second therapy phase* (20–40 min of seizure activity): If no response to benzodiazepines, use one of these options: fosphenytoin, valproic acid, or levetiracetam.
- *Third therapy phase* (40–60 min of seizure activity). If second phase therapy fails to control seizures, treatment considerations include repeating alternative second-line therapy and phenobarbital or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol combined with continuous EEG monitoring.

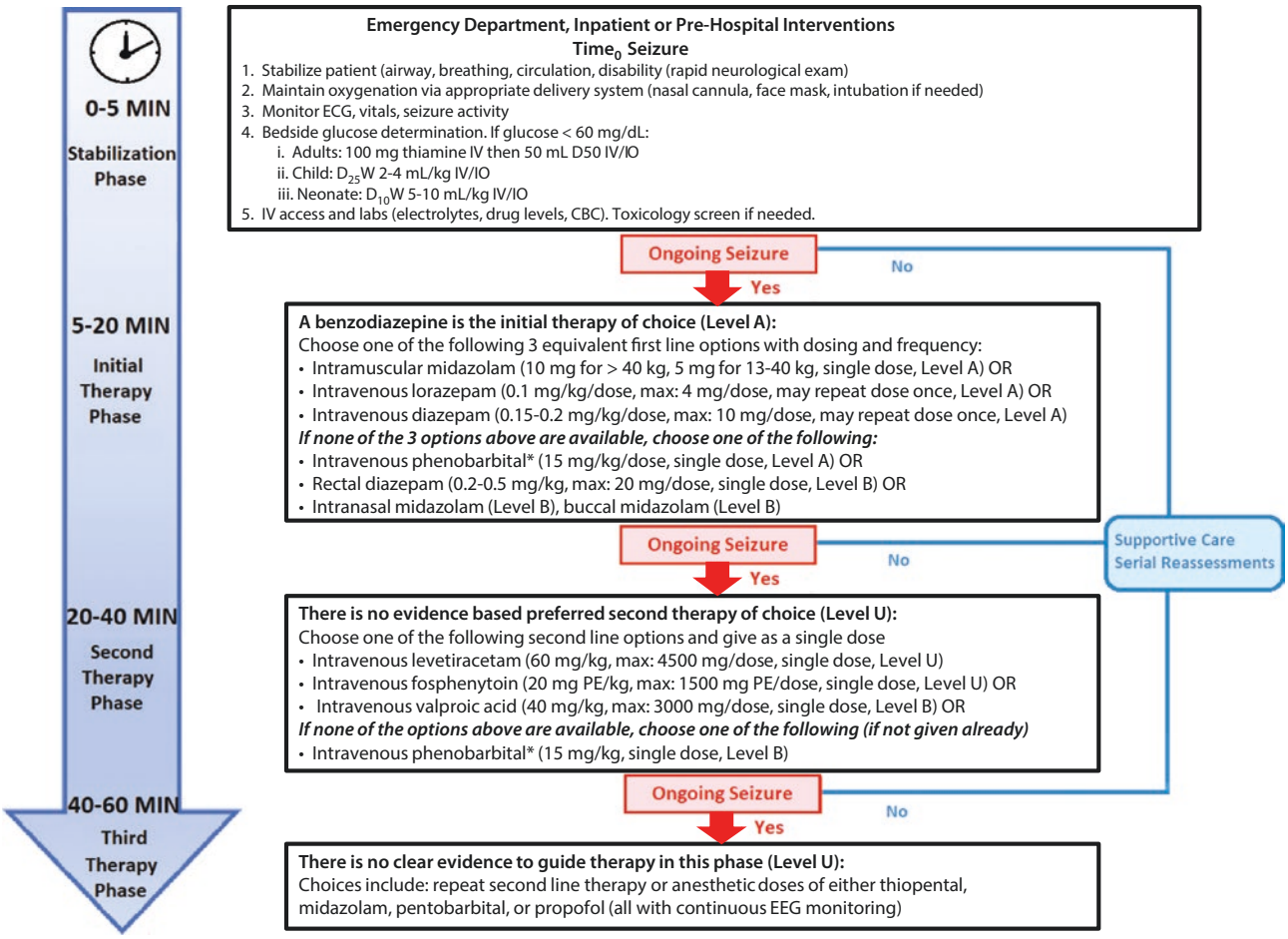

Fig. 26.4 Algorithm for the management of status epilepticus. (Adapted from American Epilepsy Society Guideline (2016). *Phenobarbital may have greater efficacy in terminating SE in neonates and infants). *ECG* electrocardiogram, *CBC* complete blood cell count, *max* maximum, *PE* phenytoin sodium equivalents, *EEG* electroencephalogram, *IV* intravenous, *IO* intraosseous. Recommendation Level: Level A - Should be done or should not be done; Level B - Should be considered or should not be considered; Level U - No recommendation. Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytical framework for evaluating and treating patients with status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate

After establishing basic life support, the treatment strategy for SE involves administration of medications to rapidly halt seizure activity followed by loading with longer-acting agents to prevent seizure recurrence while searching for correctable causes of the seizure activity.

During CSE and NCSE, maintenance of an intact airway with sufficient ventilation and oxygenation is of the utmost importance. It should be emphasized that the 30 min threshold for seizure-induced brain damage noted in animal studies was observed while the animals were fully supported from a respiratory and cardiovascular standpoint. It is indisputable that insufficient ventilation or oxygenation will worsen the clinical outcome after seizures and place the child at increased risk for anoxic/hypoxic brain injury. Therefore, clinicians should be vigilant in assessing the child's respiratory condition and intervene (bag mask ventilation, endotracheal intubation) prior to the development of hypoxemia.

Benzodiazepines are the first-line agent to treat SE.

Benzodiazepines are the first-line agent to treat SE of both categories for several reasons. Midazolam, lorazepam, and diazepam have almost immediate bioavailability to the brain once administered and enhance γ-aminobutyric acid (GABA) inhibition of neuronal excitation. At recommended dosages, these agents have relatively mild cardiovascular effects (i.e., relatively low risk of hypotension or low cardiac output), and their onset of action is within 3 min after intravenous dosing. With increased doses, the risk of hypoventilation is substantial, and preparations for maintenance of the airway should be undertaken.

Phenytoin (fosphenytoin) is frequently used in benzodiazepine-refractory CSE. Because it has a very high lipid solubility, substantial brain levels of phenytoin are achieved within 10 min of intravenous administration. Phenytoin is thought to act as an antiepileptic by blocking several ion channels, especially sodium. Phenytoin blockade causes an *increase in the voltage threshold* for cell depolarization, especially with high-frequency stimulation. Thus, blockade of Na+ channels results in inhibition of neuronal propagation of high-frequency action potentials. In the cardiovascular system, blockade of similar channels may lead to dysrhythmia, which is phenytoin's main adverse effect. The cardiovascular effects are also caused by propylene glycol used to dissolve the drug; rapid infusion of propylene glycol may cause hypotension and/or bradycardia, so phenytoin must not be infused any faster than 1 mg/kg/min. Phenytoin is also very alkaline and irritating to the vein, so the infusion is best given through a large peripheral or preferably a central venous catheter. Phenytoin has no effect on respiratory effort, cardiac contractility, or vasomotor tone, a considerable advantage over benzodiazepines.

The pro-drug of phenytoin, fosphenytoin, is water soluble thereby eliminating the need to use propylene glycol. Thus, the use of fosphenytoin limits cardiac toxicity, allows for more rapid infusion rates, diminishes the risk of peripheral IV injury from phenytoin, and permits intramuscular drug administration. Although fosphenytoin is frequently considered standard of care for benzodiazepine-refractory CSE, a recent multicenter randomized controlled study in adults did not demonstrate either superior efficacy or reduced side effects when compared to valproate and levetiracetam. Many institutions, therefore, may use these agents interchangeably in their CSE treatment protocols, especially since phenytoin is highly protein bound, which may result in toxicity if only total phenytoin concentration is monitored. Since critically ill patients often have low albumin concentrations, the total concentration may be in the normal range, but the free concentration may be toxic. Ideally, free phenytoin concentration should be monitored to guide therapy.

Administration of phenobarbital after prior administration of benzodiazepines increases the likelihood of respiratory failure from apnea or hypoventilation.

Phenobarbital had been a mainstay of therapy for infants and children with SE for decades, although it now is more commonly used as a therapy choice after benzodiazepines and phenytoin. Phenobarbital was first synthesized in 1911 and acts by facilitating the actions of GABA, the inhibitory neurotransmitter mentioned above. Phenobarbital allosterically binds to the $GABA_A$ receptor, causing an increase in Cl^- flux and hyperpolarization of the

cellular membrane, thereby inhibiting propagation of action potentials. Consistent with traditional teaching, recent evidence suggests that phenobarbital may have greater efficacy in terminating SE in neonates and infants. Phenobarbital can adversely affect cardiac performance by an indirect effect mediated by its action to reduce sympathetic nervous system activity as part of its general CNS depressant effects; the net result is the potential to decrease contractility and relax arterial and capacitance venous tone, decreasing afterload and preload. Phenobarbital is a hepatic enzyme inducer, and thus, may lower other drug levels. It has a half-life of up to 72 h, which can be longer in children with hepatic dysfunction. Administration of phenobarbital after prior administration of benzodiazepines increases the likelihood of respiratory failure.

The antiseizure mechanism of valproic acid (VPA) is not fully understood but is believed to be secondary to its ability to modulate ion channels and GABA levels. VPA decreases neuronal firing by blocking voltage-gated sodium, potassium, and calcium channels. VPA increases GABA synthesis by activating glutamic acid decarboxylase and decreasing GABA breakdown by inhibiting GABA aminotransferase. VPA adverse effects include hypotension, thrombocytopenia, pancytopenia, platelet dysfunction, hypersensitivity reactions, pancreatitis, and hyperammonemia. Hepatotoxicity is possible especially in children less than 2 years of age who are receiving other anticonvulsants or have concomitant mitochondrial or metabolic disorders. Contrary to phenobarbital, VPA is a hepatic enzyme inhibitor and thus may raise other drug levels.

Levetiracetam is structurally unrelated to any other antiepileptic class and has a novel mechanism of action. The full mechanism of action is unknown, but experimental data suggest that it binds to a presynaptic vesicle protein, which inhibits neurotransmitter release. A recent large multicenter trial compared levetiracetam to phenytoin as second-line treatment for CSE in children presenting to the emergency department. Seizures stopped in 70% of the levetiracetam group vs. 64% in the phenytoin group, which was not significantly different, but its ease of use and lack of cardiovascular side effects have caused many centers to use levetiracetam as the second-line agent for the treatment of SE. Another advantage of levetiracetam is that patients can be readily transitioned to a well-absorbed oral form which is available as a solution. Unlike other anticonvulsants, its metabolism is independent of the hepatic cytochromes, thereby eliminating the potential for pharmacokinetic interaction with anticonvulsants and other drugs (e.g., hormonal contraception). Levetiracetam has a very rapid onset of action increasing its utility in SE management.

Levetiracetam is well tolerated with minor side effects that include fatigue, somnolence, and dizziness. However, neuropsychiatric side effects in children can become problematic and include aggression, which is the most common reason for drug discontinuation. Since the drug is largely eliminated unchanged by the kidney, dose adjustment is needed in children with renal dysfunction.

When first- or second-line therapies for SE fail to stop either convulsive or electrical seizure activity (refractory SE), more aggressive measures are required to break the seizure cycle. Continuous infusions of benzodiazepines (midazolam or lorazepam), barbiturates (pentobarbital), or general anesthetics (propofol) have been utilized, usually based on institution preference since there are no conclusive studies showing the superiority of one agent or class of agents over another. In general, institution of any of these alternatives increases the likelihood of cardiorespiratory instability and requires close monitoring with intra-arterial blood pressure monitoring and often mechanical ventilation. In recent years, benzodiazepine infusions have become more common for

the treatment of refractory SE because they produce relatively fewer hemodynamic side effects. Pentobarbital infusion is still common for refractory SE; however, hemodynamic instability should be expected, and invasive hemodynamic monitoring is usually required. Use of long-term propofol infusions has been limited in children due to concerns regarding the risk of propofol infusion syndrome, which is characterized by mitochondrial dysfunction leading to cardiomyopathy, lactic acidosis, rhabdomyolysis, and kidney failure that often leads to death. As stated earlier, once seizure control is achieved, maintenance medication is required to prevent seizures and subsequent CSE. It is worth noting that even though agents like midazolam and pentobarbital are characterized as short-acting, that is referencing the short-term effects produced by rapid redistribution of the drug from the brain to other lipid-soluble tissues following a bolus dose. With prolonged infusion, all of these agents have a prolonged (often >24 h) terminal elimination.

26.4 Disorders of Muscular Tone and Strength: Infants

The hypotonic, often termed "floppy," infant or child presents a diagnostic challenge. Hypotonic infants may present with life-threatening respiratory insufficiency or failure. A detailed understanding of the differential diagnosis of the hypotonic infant is important to initiate therapy that is prompt and specific to each disorder.

Congenital myopathies are relatively rare genetic syndromes that cause abnormal muscle cell development and present with generalized weakness. Primary disorders of the motor neuron, particularly spinal muscular atrophy (SMA), can also lead to children with abnormal motor tone.

Congenital myopathies are relatively rare genetic syndromes involving abnormal muscle cell development and present with generalized weakness. Primary disorders of the motor neuron, particularly spinal muscular atrophy (SMA), also lead to abnormal motor tone. Disturbances at the neuromuscular junction can also lead to decreased movement and muscular tone. In infancy and early childhood, infantile botulism is the most common cause of acquired hypotonia.

Central core disease (CCD) is one of the most common congenital myopathies described; it typically presents in infancy with hypotonia and motor developmental delay. CCD is characterized by proximal weakness that is pronounced in the hip girdle. Orthopedic complications are common and include hip dislocation, kyphoscoliosis, joint contractures, and foot deformities. The degree of muscle weakness can vary widely with some children only minimally affected, while others will never ambulate. CCD is diagnosed on muscle biopsy by the demonstration of clearly delineated rounded areas, devoid of oxidative enzymes that are extended over the length of type I muscle fibers. Typically, the cores are centrally located, but may be dispersed in some cases. Under electron microscopy, mitochondria are absent from these rounded cores, and there is some degree of disintegration of the contractile fibers. CCD is inherited as an autosomal dominant trait with variable penetrance that was mapped to 19q12–13.2. This region contains the ryanodine receptor gene (RYR1), a key channel that mediates calcium release in response to depolarization of the muscle cell during contraction. This has relevance to anesthesia and critical care because CCD is highly associated with the development of malignant hyperthermia. The clinical course is generally non-progressive, but some children seem to worsen slowly over time.

Nemaline myopathy is characterized by subsarcolemmal, intermyofibrillar, or intranuclear rod-like structures that are reactive for α-actinin.

Nemaline myopathy is characterized by subsarcolemmal, intermyofibrillar, or intranuclear rod-like structures that are reactive for α-actinin. These rods can be found in either the type I or type II muscle fibers and are distributed asymmetrically between muscle groups within an affected individual. Electron microscopy reveals that the rods are in continuity with the Z lines. The number

of rods in each muscle does not correlate with clinical severity of the disease. Five mutations have been identified in children with nemaline myopathy, although none of the mutations occurs within the α-actinin gene. Children with nemaline myopathy show generalized weakness and facial anomalies, particularly high-arched palate. Skeletal involvement, including arthrogryposis multiplex complex and scoliosis, is common as is cardiac involvement in later life. Severe neonatal, milder congenital, and late-onset forms of the disease are inherited as an autosomal recessive trait, while the childhood-onset form of disease is inherited as an autosomal dominant gene.

Multi-minicore disease (MmD) is characterized by multiple small areas of disorganization within the sarcomere. These areas lack oxidative capacity and affect both fiber types (usually with type I predominance). Recent studies indicate that minicores may progress to classical cores seen in CCD, suggesting that these two diseases may represent a continuum of a common syndrome. Mutations in several genes, including RYR1, have been demonstrated in MmD, again suggesting a continuum between the two diseases. Four relatively homogeneous presentations of MmD have been described. The "classic" form features axial and respiratory muscle weakness, scoliosis, and limb joint hyperlaxity and is relatively non-progressive. The ophthalmoplegic form features severe facial weakness along with the generalized hypotonia of the other syndromes. The "early-onset" form is associated with arthrogryposis, and the "slowly progressive" form specifically affects the muscles of the hand to a greater extent than the other forms. All four forms tend to show autosomal recessive inheritance, but this has not been definitively determined.

Children with central core and multi-minicore disease may have genetic abnormalities in the RYR1 gene, which also places them at risk for malignant hyperthermia.

Myotubular myopathy (MTM) is the most severe congenital myopathy and has an X-linked inheritance pattern. Histologically, small myofibers with central nuclei resembling fetal myotubes are found on muscle biopsy of children with MTM. Mutations in the myotubularin (MTM1) gene (chromosome Xq28) are responsible for all cases of MTM, leading to abnormal phosphorylation of the lipid second messenger phosphatidylinositol 3-phosphate. Over 140 mutations have been described in this gene, with 5 exons accounting for over 70% of the cases (exons 4, 8, 9, 11, 12). Point mutations lead to truncated forms of the protein, often causing a clinically severe phenotype. Missense mutations account for approximately 25% of the cases and are generally associated with a slightly milder phenotype.

Myotubular myopathy is the most severe congenital myopathy and shows an X-linked inheritance pattern.

The onset of symptoms is usually during early infancy with severe hypotonia and lack of spontaneous movement. Severity can range from mild to life-threatening; most affected children have a severe form of the disorder requiring chronic mechanical ventilation. Feeding difficulties and respiratory failure are not uncommon. Hip and knee contractures, facial involvement, and limited extraocular muscle movement are present in some infants as well as accelerated bone aging, mild spherocytosis, and hepatic peliosis in long-term survivors. Female heterozygotes are often asymptomatic but may exhibit subtle signs of muscle weakness.

SMA is inherited in an autosomal recessive manner and leads to weakness and decreased movement due to progressive apoptosis of anterior motor horn neurons. Over 97% of SMA patients have mutations in the survival motor neuron gene (SMN1) on chromosome 5q13, resulting in deficiency of the SMN1 protein. Loss of this gene product leads to apoptotic cell death in spinal motor neurons, the pathological feature of the SMA disease subtypes. SMA has three principal types of presentations with overlap between them. *Type I*, also known as *Werdnig-Hoffman disease*, presents in the first few months of life and is the most severe subtype with death by 2 years of age if chronic mechanical ventilation is not provided. *Type II* SMA presents after the first 6 months of life and

SMA is inherited in an autosomal recessive manner and leads to weakness and decreased movement due to progressive apoptosis of anterior motor horn neurons.

is less severe. Affected children achieve some motor milestones (such as sitting independently) but still face a substantially decreased life expectancy. *SMA type III*, also known as *Kugelberg-Welander disease*, presents after 18 months of age; affected children become weaker throughout childhood and adolescence.

SMA should be considered in any infant with unexplained weakness or hypotonia. A history of motor difficulties, loss of motor skills, and proximal muscle weakness is often elicited. Examination findings include hyporeflexia or areflexia, tongue fasciculations, and signs of lower motor neuron dysfunction. Genetic analysis can confirm the diagnosis of SMA by identifying mutations in the SMN1 gene.

In late 2016, the FDA approved nusinersen (Spinraza) to treat infants and children with SMA. Nusinersen is an antisense oligonucleotide designed to treat SMA caused by mutations in chromosome 5q13 that lead to SMN protein deficiency. The drug modifies splicing of the SMN2 gene to increase production of normal SMN1 protein. Recent trials demonstrated improvements in motor milestones in over half of the infants treated with this disease-modifying therapy. Nusinersen requires intrathecal administration every 4 months and is generally well tolerated. An increasing number of states now include SMA as part of the newborn screening process to facilitate early treatment. In 2019, the FDA approved Zolgensma, which replaces the defective gene with the SMN1 gene delivered by an adeno-associated viral vector. A single intravenous injection in infants less than 2 years of age appears to result in a long-standing cure, but since it is new, these patients will need to be monitored.

Botulism is a paralytic disease caused by release of one of the eight immunologically distinct toxins from the bacteria, Clostridium botulinum.

Botulism is a paralytic disease caused by release of one of the seven immunologically distinct toxins from the bacteria *Clostridium botulinum*. Though there are some biochemical differences between the toxins, all prevent the release of acetylcholine at the neuromuscular endplate following neuronal depolarization. The toxins also prevent release of acetylcholine at other sites within the autonomic nervous system, explaining other symptoms such as dry mouth and decreased sweating. Although older children can be affected by botulism by ingesting improperly stored food, by absorbing the toxin from an improperly cleaned wound, or as a bioterrorism event, infantile botulism presents as a unique disease during the first year of life. Infants with botulism ingest spores that were aerosolized either from soil or from infected food sources, most notably honey. Due to changes in intestinal bacterial flora, infants may be at particular risk when transitioning from breast- to formula-feeding, allowing the *Clostridia* to multiply and produce toxin within the intestine that is subsequently absorbed. Botulinum toxin acts by binding presynaptically to high-affinity recognition sites on cholinergic nerve terminals, which decreases the release of acetylcholine, causing a neuromuscular blocking effect. The effect is long-lasting with recovery occurring through proximal axonal sprouting and muscle re-innervation by formation of a new neuromuscular junction. Some data suggest there is also regeneration of the original neuromuscular junction.

The earliest sign is constipation that may be protracted. A descending paralysis, almost invariably including some or many of the cranial nerves, is the characteristic pattern of physical findings. Bulbar findings include a weak cry, poor suck, and bilateral ptosis. Loss of airway reflexes coupled with progressive muscular hypotonia often leads to respiratory failure. The paralysis can last for weeks, and therefore critical care requires meticulous attention to pulmonary toilet, nutrition, and avoidance of nosocomial infection. Epidemiological studies suggest regions within the country that are at particularly high risk of infantile botulism.

Botulism is diagnosed clinically (the descending nature of the paralytic course) and confirmed with electrophysiological tests (normal sensory nerve amplitudes, normal nerve conduction studies, a decremental response of muscle action potential, an increased number of brief, polyphasic motor unit action potentials). Botulinum toxin can also be recovered from stool samples of affected children, provided a sample can be obtained early in the illness.

Intravenous botulism immune globulin (IV-BIG) is both safe and effective in the treatment of infantile botulism. IV-BIG decreases the need for mechanical ventilation, duration of intensive care unit (ICU) and hospital stay, and overall cost of care. IV-BIG binds to circulating neurotoxins and prevents binding to the neuromuscular junction. However, the antitoxin cannot reverse neurotoxin binding that has already occurred; therefore, administration early in the course of disease is critical. Aminoglycosides should be avoided in children with botulism (or other diseases with muscle weakness such as myasthenia gravis), as these agents have intrinsic neuromuscular blocking effects that exacerbate the effect of the toxin and lead to prolongation of the paralysis.

Aminoglycosides should be avoided in children with botulism and other conditions with muscle weakness, such as myasthenia gravis, as these agents exacerbate the effect of the toxin and lead to prolongation of the paralysis.

The above disorders represent a diverse spectrum of illnesses; thus, the history and physical exam must be used to focus the diagnostic testing. The diagnosis of generalized myopathy can be confirmed by abnormal electromyography (decreased amplitude) with normal nerve conduction studies. However, definitive diagnosis often requires histological analysis of muscle tissue and/or genetic testing.

Treatment of infants with neuromuscular weakness is mainly supportive in nature while awaiting diagnosis. Careful assessment of cranial nerve function, particularly those associated with airway reflexes, is essential to prevent aspiration. Assessing both the adequacy of ventilation and the ability to maintain functional residual capacity for oxygenation are keys toward management of these infants' respiratory insufficiency. Special care must be taken in infants with CCD and MmD to avoid agents that may cause malignant hyperthermia.

26.5 Disorders of Muscular Tone and Strength: Older Children and Adolescents

Acquired diseases leading to weakness in older children include transverse myelitis, Guillain-Barré syndrome (GBS), myasthenia gravis, critical illness neuropathy/myopathy, and skeletal muscle channelopathies. It is useful to categorize diseases of acute neuromuscular weakness according to the localization of the pathologic process, such as spinal cord, peripheral nerve, neuromuscular junction, or muscle (Table 26.2).

Transverse myelitis (TM) is a heterogeneous disorder of the spinal cord that affects sensory, motor, and autonomic function and is believed to be predominantly inflammatory in nature. The pathogenesis of the neuroinflammation in TM is poorly understood but may involve postinfectious, postvaccination, autoimmune, or idiopathic phenomenon. Pathologically, the inflammation can involve both gray and white matter. Unlike GBS, TM is not a pure demyelinating disorder but rather a mixed inflammatory disorder that affects neurons, axons, oligodendrocytes and myelin.

A bimodal age distribution has been observed; children under 5 and older than 10 years of age are more likely to be affected. In addition to evaluation for systemic inflammatory conditions, patients with TM should be evaluated for aquaporin-4 IgG and MOG antibodies. A consensus group recently established diagnostic criteria for TM that includes signs of sensory, motor, or autonomic spinal cord dysfunction, a sensory level, proof of inflammation within the spinal cord (MRI or CSF evidence), and the progression to a functional

Table 26.2 Disorders of neuromuscular weakness

Disorder	Location	Pathology	Findings	Treatment
Encephalopathy	Cerebral cortex/ brainstem	Direct neuronal injury	Altered sensorium, upper motor neuron findings, and possible focality; seizure; movement disorder; autonomic instability	Treatment of underlying cause (e.g., metabolic, infectious, inflammatory) and neuroprotective strategies Inflammatory: 1st Line: Steroids; IVIG; plasmapheresis 2nd Line: rituximab, cyclophosphamide, other immunosuppressive agents
Transverse myelitis	Spinal cord	Unclear; likely multifactorial inflammatory and/ or vascular etiology	Bilateral sensory, motor, or autonomic spinal cord dysfunction, a sensory level and radiographic proof of inflammation within the spinal cord. Progression to a functional nadir within 4–21 days from onset of symptoms	High-dose steroids +/−plasmapheresis[a]; consider IVIG
Acute flaccid myelitis	Anterior horn cell	Unclear; high association with certain strains of enterovirus	Sudden arm or leg weakness and loss of muscle tone and reflexes; "polio-like condition"; frequently preceded by respiratory illness or fever	Supportive Consider IVIG, plasmapheresis, or steroids on case-by-case basis[b]
Spinal muscular atrophy	Anterior horn cell	Mutations of chromosome 5q13 lead to apoptotic anterior horn cell death	Dependent upon subtype: rapid (type I) to chronic (type III) loss of motor function	Supportive care; Nusinersen; Zolgensma (onasemnogene abeparvovec-xioi)
Guillain-Barré syndrome	Peripheral nerve	Immune-mediated injury to the myelin sheath covering of the peripheral nerve	Rapidly ascending paralysis with areflexia Miller-Fisher syndrome characterized by ataxia ophthalmoplegia and areflexia Dysautonomia not uncommon	Supportive care (may include mechanical ventilation) and plasmapheresis or IVIG
Botulism	Neuromuscular junction	Presynaptic binding of toxin prevents release of AcH into the NMJ	Constipation in infants. Descending paralysis with early bulbar findings (weak cry, poor suck, and bilateral ptosis). Progression to respiratory failure common	Supportive care (may include mechanical ventilation) and botulism immune globulin
Myasthenia gravis	Neuromuscular junction	Autoantibodies to the postsynaptic AchR lead to receptor blockade and destruction	Fluctuating or fatigable weakness. Decreased muscle contraction is observed with progressive muscle work. Ocular and bulbar weakness common	Acetylcholinesterase inhibitors, immunosuppression and thymectomy
Organophosphate poisoning	Neuromuscular junction	Inhibition of acetylcholinesterase in the NMJ increases available AcH, which leads to a depolarizing neuromuscular blockade	Combination of excessive muscarinic and nicotinic effects: muscle weakness with diarrhea, urination, miosis, bronchorrhea, emesis, lacrimation, and salivation (DUMBELS)	Support airway, breathing and circulation, decontamination, atropine and pralidoxime

Table 26.2 (continued)

Disorder	Location	Pathology	Findings	Treatment
Tick paralysis	Neuromuscular junction	Neurotoxin prevents release of AcH into the NMJ	Symmetrical ascending paralysis with areflexia Mimics GBS	Tick removal Supportive
Skeletal muscle channelopathies	Muscle	Disorders associated with mutations in sodium, potassium, and calcium ion channels leading to hypoexcitability and periodic paralysis	Acute episodic weakness usually manifesting during rest after prolonged exercise. Associated potassium abnormality based on subtype	Supportive Carbonic anhydrase inhibitor for specific subtypes

[a]High-dose steroids may be given alone or in combination with plasmapheresis for the treatment of acute transverse myelitis
[b]The Centers for Disease Control and Prevention recommends supportive care with consideration of steroids, IVIG, or plasmapheresis on a case-by-case basis. IVIG is intravenous immunoglobulin; AcH is acetylcholine; NMJ is neuromuscular junction; AchR is the acetylcholine receptor; and GBS is Guillain-Barré syndrome

nadir within 4 h–21 days from the onset of symptoms. MRI with gadolinium enhancement is the preferred imaging. CSF studies should include cell count, IgG index, and analysis for oligoclonal bands. Although there are no FDA-approved treatments, high-dose corticosteroids are frequently used with or without concurrent administration of plasmapheresis. IVIG may also be considered in lieu of or following plasmapheresis. Treatment considerations are based on the experience reported from open-label studies and retrospective analyses, primarily involving adult patients. The prognosis is variable with children generally having better outcomes than adults. Recovery is arduous and may begin between 2 and 12 weeks after the onset of symptoms. Full recovery may take years and permanent sequelae are not uncommon.

Acute flaccid myelitis (AFM) is a poorly understood syndrome that is frequently referred to as a "polio-like syndrome" owing to its similar clinical appearance. Often, a viral prodrome is reported within days to weeks preceding the onset of the weakness. AFM is clinically diagnosed by the acute onset of focal limb weakness with MRI findings demonstrating a spinal cord lesion primarily of the gray matter and spanning one or more spinal segments. Children with gray matter lesions in the spinal cord resulting from malignancy, vascular disease, or anatomic abnormalities should be excluded. The weakness can be profound, and motor involvement can be varied among affected children. A review of nearly 200 children with AFM revealed involvement of 1 or 2 limbs in 55 percent of cases and 3 or 4 limbs in 45 percent of cases. Cranial nerve dysfunction and altered mental status are not uncommon, present in up to one third of children.

Based on the Centers for Disease Control and Prevention (CDC) data, there have been over 600 confirmed cases of this rare condition since 2014. There appears to be a cyclic occurrence pattern with an increased number of cases every 2 years (i.e., 2014, 2016, 2018); peak incidence is between summer and fall. The cyclic nature suggests a viral association, and clinical studies suggest an association with infection by enterovirus D68, adenovirus, and West Nile virus.

The CDC recommends early specimen collection (within 24 h of symptom onset) of CSF, serum, stool, and nasopharyngeal swab in patients under investigation for AFM to maximize the likelihood of identifying the etiology.

Characteristic features of AFM include a febrile or respiratory illness that precedes the onset of neurologic symptoms, acute flaccid limb weakness with evolution of weakness over hours to days, and magnetic resonance imaging (MRI) evidence of predominantly gray matter involvement in the spinal cord.

Neuroimaging of the entire central nervous system should be performed. MRI may be unremarkable in the first 72 h, and cases may be mistaken for GBS. Therefore, repeat MRI may be necessary. CSF demonstrating pleocytosis is supportive for the diagnosis of AFM.

Treatment is primarily supportive; the CDC currently states that there is "no indication that any specific targeted therapy or intervention should be either preferred or avoided in the treatment of AFM. There are currently no targeted therapies/interventions with enough evidence to endorse or discourage their use for the treatment or management of AFM." In a mouse model infected with enterovirus D68, there was suggestion that steroids may be harmful, which raised concern for translation to humans. The possible benefits of corticosteroids to manage spinal cord edema or white matter involvement in AFM should be balanced with the potential harm of immunosuppression in the setting of possible viral infection. Although long-term outcomes are lacking, neurologic recovery is variable and often incomplete. Children with AFM are more likely to have persistent neurologic deficits, as opposed to other causes of myelitis; more than half of all children with confirmed AFM have persistent motor deficits.

Guillain-Barré syndrome is characterized by a rapidly ascending paralysis that lasts for several weeks or longer and has been subdivided into subtypes based on clinical features and histopathological findings.

Guillain-Barré syndrome (GBS) is an immune-mediated polyneuropathy that is the leading cause of flaccid paralysis in the Western Hemisphere with an annual incidence of 1.5 per 100,000. GBS is characterized by a rapidly ascending paralysis that can persist for several weeks or longer. GBS has been divided into subtypes based on clinical features and histopathological findings. The pathogenesis of GBS is still unclear, but humoral and cellular immune mechanisms have been implicated based on (i) activation of complement and deposition of membranolytic factors on myelin sheaths, (ii) the presence of circulating anti-ganglioside or glycolipid antibodies, (iii) an increase in T-cell activation products and cytokines, and (iv) invasion of the myelin sheath by activated macrophages.

An antecedent infection is common. Campylobacter, cytomegalovirus, Epstein-Barr virus, mycoplasma pneumoniae, and influenza have all been implicated as a trigger. The infection usually precedes the onset of symptoms by approximately 1–3 weeks.

The presentation of GBS varies based on the subtype but classically is heralded by paresthesia in the toes and fingertips followed by lower extremity weakness or neuropathic pain. The weakness ascends over hours to days to involve the arms and, in severe cases, the muscles of respiration. Weakness or pain of the lower extremity often manifests as a child's refusal to walk.

Over half of the children with GBS develop autonomic dysfunction, which may include cardiac dysrhythmias, episodic hypertension, ileus, urinary retention, and sweating. Examination reveals abnormal gait (if ambulatory), symmetric weakness with diminished or absent reflexes, pain with movement, and typically no loss of sensation.

GBS can be divided into five distinct subtypes, though other unusual presentations have been described. The classic GBS subtype presents with ascending flaccid paralysis and is designated acute inflammatory demyelinating polyneuropathy (AIDP). This subtype represents the most common presentation in Europe and the United States, and histopathological analysis of peripheral nerves reveals extensive macrophage-mediated demyelinated lesions and intense T-cell infiltration. Acute motor axonal neuropathy (AMAN) is a subtype that presents with pure motor symptoms because only motor axons become demyelinated. AMAN is the most prevalent form of GBS in China and affects children and young adults in summer epidemics. An axonal variant that affects both sensory and motor axons is termed acute motor and sensory axonal neuropathy (AMSAN). AMSAN has a greater sensory component

than AIDP and generally has a more severe clinical course. Histologically, AMAN and AMSAN are distinguished from AIDP by their lack of T-cell lymphocyte infiltrates. The Miller-Fisher syndrome (MFS) is a distinct form of GBS that is characterized by ophthalmoplegia, ataxia, and areflexia and can transition into classical AIDP in a proportion of cases.

Confirmation of the diagnosis is largely based on clinical symptoms with some reliance on ancillary testing. Cerebrospinal fluid analysis at the end of the first week of illness normally demonstrates an acellular increase in protein concentration. Recent studies suggested that the lipopolysaccharide of *Campylobacter jejuni* may mimic the nervous system gangliosides GM_1, GD_{1a}, GD_3, and GT_{1a} and this molecular similarity may be responsible for the production of anti-ganglioside antibodies observed in GBS. However, since only about 50% of patients with GBS demonstrate antibodies against GM_1, this test is relatively specific but not sensitive. Electrophysiological studies demonstrate abnormal nerve conduction in the distribution of symptoms observed clinically. Recently, more extensive electrophysiological testing, measuring differences in axonal excitability, reportedly can distinguish between the various subtypes of GBS.

Cerebrospinal fluid analysis in patients with GBS at the end of the first week of illness normally demonstrates an acellular increase in protein concentrations.

Treatment for GBS involves cardiopulmonary supportive care followed by immunotherapies. Determining that the child can maintain an airway and appropriate gas exchange is essential. Measurements of respiratory mechanics in the cooperative child, including vital capacity, have been used clinically to follow subtle changes in respiratory muscle mechanics.

Serial pulmonary function testing (PFT) in the cooperative older child can identify children who are at risk for respiratory failure and require intubation. Serial measurements identifying at risk children include:

- Vital capacity ≤20 mL/kg
- Maximum inspiratory force less negative than −30 cmH_2O (i.e., the more subatmospheric, the better)
- Maximum expiratory pressure ≤40 cmH_2O
- Tidal volume <5 mL/kg.

These PFT parameters can be remembered as the "20/30/40 rule." The child is at risk of respiratory failure if the vital capacity is <20 mL/kg, the maximum inspiratory pressure is less negative than −30 cmH_2O, or the maximum expiratory pressure is <40 cmH_2O.

20/30/40 rule: Child with GBS is at risk of respiratory failure if the vital capacity is <20 mL/kg, the maximum inspiratory pressure is less negative than −30 cmH_2O, or the maximum expiratory pressure is <40 cmH_2O.

In children too young or unable to cooperate, clinical signs of impending respiratory failure include inability to lift their head when supine, bulbar symptoms, tachypnea, increasing oxygen requirement, increasing use of accessory muscles, and hypercarbia; the latter is often a late finding.

The immunotherapies for GBS include plasmapheresis (i.e., plasma exchange) and administration of intravenous immunoglobulin (IVIG). IVIG and plasma exchange for children with GBS should be reserved for symptomatic children with progressive weakness that may be manifested as worsening respiratory distress, bulbar dysfunction, and/or inability to walk unaided. Plasmapheresis is thought to improve clinical symptoms by physically removing the causative autoantibodies from the serum by simple serum replacement. IVIG is thought to improve GBS symptoms by complex mechanisms that are not completely understood, but data suggest it suppresses further autoantibody formation and reduces T-cell and macrophage activation of the immune system. IVIG is often the initial immunomodulation chosen in children because of its relative safety and ease of use. However, there are no convincing data suggesting that IVIG is superior to plasmapheresis. In a study of 463 patients, IVIG and plasma exchange were found to be equally effective regarding motor improvement at 4 weeks after clinical onset; combination therapy with both

The immunotherapies for Guillain-Barre syndrome include plasmapheresis (plasma exchange) and administration of intravenous immunoglobulin.

The pathognomonic feature of myasthenia gravis is fluctuating or fatigable weakness, whereby decreased muscle contraction is observed with progressive muscle work.

IVIG and plasma exchange was not superior. Optimization of IVIG dosing has been studied in recent years; current recommendations are for a total IVIG dose to 2 g/kg, given as 1 g/kg for 2 days or 400 mg/kg per day for 5 days. Systemic administration of corticosteroids has failed to demonstrate efficacy in GBS in several studies and should be avoided.

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction that has been described for over three centuries. The first description of the disorder involved a woman with severe bulbar weakness that would improve after sleeping or rest. MG is relatively uncommon, affecting approximately 20 per 100,000 population, and is less common in children. Females are affected more often than males, with a ratio of approximately 2:1 across most longitudinal studies. The pathognomonic feature of MG is fluctuating or fatigable weakness, whereby decreased muscle contraction is observed with progressive muscle work. Ocular and bulbar weakness is the cardinal feature, yet pupillary function is generally unaffected. More generalized weakness may progress to respiratory failure requiring intensive care. Autoantibodies to the acetylcholine receptor (AchR) are demonstrable in the serum of up to 95% of patients; the destruction of AchRs at the neuromuscular junction is responsible for the weakness. Definitive diagnosis is generally made by electrophysiological and pharmacological testing. Repetitive nerve stimulation at 2–3 Hz in patients with MG yields a decremental response of compound action potentials. More definitively, the administration of a short-acting acetylcholinesterase inhibitor (edrophonium) leads to increased acetylcholine in the neuromuscular junction and a rapid, transient improvement of symptoms. Definitive treatment can include longer-acting acetylcholinesterase inhibitors, immunosuppressive therapy (prednisone, mycophenolate mofetil, azathioprine, cyclosporine, and/or cyclophosphamide), and thymectomy.

Both critical illness neuropathy and myopathy are more commonly diagnosed in adults; however, pediatric cases are appearing in the literature. Critical illness neuropathy was first described in 1984 and is highly associated with recovery from sepsis and septic shock. In some reports, up to 70% of sepsis survivors with multiple organ failure have some degree of muscular weakness leading to delays in weaning from mechanical ventilation. Flaccid weakness of the extremities and decreased deep tendon reflexes are the common physical findings. Histological analysis reveals a distal axonopathy with degeneration of both motor and sensory fibers. Electrophysiological studies show reduction or absence of compound muscle and sensory action potentials, fibrillations, and loss of motor potentials with maximal efforts. Normal nerve conduction studies distinguish between critical illness neuropathy and GBS. Critical illness myopathy presents with similar symptoms as critical illness neuropathy. However, the myopathy occurs generally after an acute respiratory illness (including acute respiratory distress syndrome and severe status asthmaticus) and is associated with the concomitant use of high-dose corticosteroids, non-depolarizing neuromuscular antagonists, and/or aminoglycosides. Histological analysis of muscle is quite variable, but disorganization of the myofibers and mild myofiber necrosis is often observed. Electrophysiological studies are generally similar to those of critical illness neuropathy, and muscle biopsy is needed to distinguish between the two conditions. There are no specific therapies for either condition, but both tend to improve over the course of several weeks to many months. These conditions are not well-characterized in children, and only sporadic case series in children exist. Adult studies suggest that prolonged neuromuscular blockade with concomitant use of either high-dose corticosteroids or aminoglycoside

antibiotics plays a role in the pathogenesis of the disorders. Continuous neuromuscular blockade may affect skeletal muscle in the same way that loss of muscle innervation after a spinal cord injury leads to muscle atrophy. Currently, not enough information exists to make precise recommendations to prevent this disorder in children, but continuous infusions of neuromuscular blockers are discouraged.

Diseases affecting muscles can produce profound weakness. These include infectious and traumatic causes of myositis. Severe myositis can accompany influenza and coxsackievirus infections, Lyme disease, and parasitic diseases such as trichinosis. Severe traumatic injury to a large area of muscle can lead to profound weakness and multiple organ dysfunction due to rhabdomyolysis.

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Skeletal muscle channelopathies are a complex and heterogeneous group of muscle disorders which present with acute weakness. These disorders are marked by abnormal ion channel activity and are often subgrouped into the nondystrophic myotonias and the periodic paralyses. The nondystrophic myotonias include myotonia congenita and are characterized by increased muscle fiber activity and impaired relaxation. Patients exhibit increased muscle fiber activity with complaints of tightness, cramping, or "locking up" when sudden muscle activity is attempted. They also experience improved strength with repetitive slow activation of a muscle group that is referred to as the "warm-up phenomenon." The molecular defect in myotonia congenita is a point mutation in the gene encoding the muscle chloride channel.

Periodic paralyses include hyperkalemic periodic paralysis (hyperPP), hypokalemic periodic paralysis (hypoPP), and the Andersen-Tawil syndrome (ATS). All share autosomal dominant inheritance and are characterized by episodic attacks of mild to severe weakness with elevations in serum creatine kinase.

Periodic paralyses include hyperkalemic periodic paralysis (hyperPP), hypokalemic periodic paralysis (hypoPP), and the Andersen-Tawil syndrome (ATS). All share autosomal dominant inheritance and are characterized by episodic attacks of mild to severe acute weakness with elevations in serum creatine kinase.

HyperPP is due to an abnormality in the sodium ion channel and is characterized by interval normokalemia with hyperkalemia during attacks. Occasionally, patients experiencing an attack may have normal potassium levels if medical attention is delayed. Triggers for hyperPP include rest after prolonged exercise, cold exposure, and high potassium intake. Avoidance of triggers, supportive care during attacks, and the prophylactic use of thiazide diuretics or carbonic anhydrase inhibitors are the mainstays of therapy.

HypoPP is due to an abnormality in the gene encoding the calcium ion channel (70%) or less commonly the sodium ion channel and is characterized by interval normokalemia with hypokalemia during attacks. Triggers for hypoPP include rest after prolonged exercise and high-carbohydrate meals. Generalized flaccid paralysis is more common than in hyperPP and may require ICU supportive care. Avoidance of triggers, supportive care during attacks, and the prophylactic use of carbonic anhydrase inhibitors and potassium-sparing diuretics are the mainstays of therapy.

ATS is a rare autosomal dominant disorder characterized by the triad of periodic paralysis, propensity toward ventricular arrhythmia, and dysmorphology. Dysmorphic features include short stature, low set ears, micrognathia, clinodactyly, and scoliosis. A prolonged QT interval is often apparent on ECG. Some patients may develop a mild fixed proximal muscle weakness between attacks. Potassium levels may be normal, low, or elevated during attacks. The molecular basis of the syndrome is several mutations in the gene encoding for inward potassium ion channels. Triggers include rest after prolonged exercise and high potassium intake. Carbonic anhydrase inhibitors and beta blockers have been used to prevent attacks. Implantation of an internal defibrillator to treat potentially fatal arrhythmias is strongly advised.

Review Questions

1. Which statement regarding acute disseminated encephalomyelitis (ADEM) is true?
   A. A causative organism is often identified using CSF culture or blood serologies.
   B. Although the pathogenesis is incompletely understood, ADEM often follows immunization.
   C. CSF examination reveals a significant pleocytosis with lymphocyte predominance.
   D. Morbidity secondary to refractory intracranial hypertension is common.
   E. Pathologic features include immune-mediated myelin damage to brain and spinal cord reminiscent of multiple sclerosis.

2. A 14-year-old female on day 6 of induction chemotherapy (daunorubicin, L-asparaginase, vincristine, and prednisone) for acute lymphocytic leukemia complains of headache and has a generalized tonic-clonic seizure. She has had no hypoxemia or poor perfusion and has normal electrolytes except for sodium of 133 mmol/L drawn 2 h prior to the seizure. She has a WBC count of 3000 cells/μL, hemoglobin 12 gm/dL, and platelet count of 27,000/μl. She was noted to have moderate hypertension for the previous 36 h that was attributed to volume loading and steroids. She is currently postictal and minimally arousable. Her vitals are as follows: pulse 78 beats per minute, BP 159/99 mm Hg, RR 20 breaths per minute, and pulse oximetry 100% on 60% face mask. Which of the following is the most likely pathogenesis of her neurologic deterioration?
   A. Acute encephalopathy secondary to focal vasogenic edema caused by alterations in endothelial integrity and autoregulation
   B. Acute intracranial infection due to immunocompromise
   C. Hemorrhagic stroke due to thrombocytopenia
   D. Hyponatremia-induced seizure and prolonged postictal state.
   E. Thrombotic stroke secondary to hypercoagulable state induced by L-asparaginase.

3. Which of the following statements regarding congenital myopathies is (are) true?
   A. Children with nemaline myopathy show generalized weakness and facial anomalies, particularly high-arched palate, and may have skeletal involvement.
   B. Infants with central core disease may present with mild to moderate hypotonia and are susceptible to malignant hyperthermia.
   C. Multi-minicore disease and nemaline myopathy share genetic and histopathologic features.
   D. Myotubular myopathy (MTM) is the most severe congenital myopathy and demonstrates an X-linked inheritance pattern.
   E. All of the above.

4. A 16-year-old male develops ascending weakness and areflexia approximately 2 weeks after having gastroenteritis. It is 4 days since the onset of his current symptoms, and Guillain-Barré syndrome is suspected. Which of the following is a true statement regarding the diagnosis of GBS?
   A. Confirmation of the diagnosis is largely based on ancillary testing.
   B. CSF analysis at day 4 will demonstrate a marked increase in protein and lymphocytes.
   C. Electrophysiological studies demonstrate abnormal nerve conduction studies in the distribution of symptoms observed clinically.

D. The differential diagnosis of Guillain-Barré syndrome includes tic paralysis, acute disseminated encephalomyelitis, and transverse myelitis.
E. The presence of anti-ganglioside antibodies is a relatively specific and sensitive ancillary test for GBS.

5. Appropriate care of the child with new-onset status epilepticus includes which of the following?
   A. Emergent MRI after stabilizing airway, breathing and circulation, and seizure control.
   B. Initial use of fosphenytoin in any seizure lasting greater than 15 min.
   C. Initial use of high-dose barbiturates in any seizure lasting greater than 15 min.
   D. Use of benzodiazepines as the initial pharmacologic intervention to control seizures.
   E. Use of combination phenytoin and barbiturate if initial benzodiazepine therapy fails.

6. A 10-year-old, 50 kg boy with known history of epilepsy, who is generally well controlled with levetiracetam 750 mg twice daily, is admitted to the PICU for increased seizure frequency. On examination, you find the child with eyes deviated to the right with generalized tonic posturing. Vital signs demonstrate tachycardia, sinus rhythm, regular respirations and 100% oxygen saturation. Bedside glucose testing is 85 mg/dL. After 5 min, you provide IV lorazepam 4 mg. The tonic posturing resolves. The eyes remain deviated to the right. What is your next step?
   A. No further pharmaceutical treatment required as the seizures have stopped.
   B. Order long-term monitoring EEG and continue to observe.
   C. Repeat IV lorazepam 4 mg, monitor airway, and prepare second-line therapy.
   D. Intubate and initiate anesthetic doses of midazolam.
   E. Emergent MRI after airway, breathing, circulation, and seizure control.

7. A 4-year-old girl is admitted due to altered mental status, described as increased sleeping with difficulty to arouse and inappropriate response to questions. Recent history of upper respiratory infection with fever 1 week ago. She is currently afebrile. There is no nuchal rigidity. Exam is limited due to mental status; however, the left side has less spontaneous movement compared to the right, and there is a positive Babinski on the left. What are the best next steps?
   A. MRI brain with and without contrast, lumbar puncture, and serum anti-MOG.
   B. Start IV steroids and IVIG.
   C. Electroencephalogram and administer one-dose IV benzodiazepine.
   D. MRI spine with and without contrast.
   E. Start broad-spectrum IV antibiotics at meningitis dosing.

8. A 13-year-old female develops facial weakness, impaired extraocular movements, and ataxia approximately 2 weeks following a bout of gastroenteritis. It is 4 days since the onset of her current symptoms, and Guillain-Barré syndrome (GBS) is suspected. Which of the following supports the diagnosis of GBS?
   A. MRI of the brain demonstrates diffuse gadolinium enhancement of the cerebellum.

B. CSF analysis demonstrates a marked increase in protein with normal lymphocytes.
C. MRI spine demonstrates a longitudinally extensive (more than 3 vertebral segments) gadolinium-enhancing lesion in the white matter.
D. Repetitive nerve stimulation at 2–3 Hz in patients with GBS yields a decremental response of compound action potentials.
E. None of the above.

9. A 10-year-old boy male with neurofibromatosis presents with altered mental status and right-sided weakness. A stroke code is called, and an urgent MRI without contrast is performed which reveals an acute left MCA infarct, as well as multifocal subacute lacunar infarcts. What additional testing should be performed and what are you evaluating for?
A. CT head – Evaluate for hemorrhage.
B. MR venogram – Evaluate for venous thrombosis.
C. MRI brain with contrast – Evaluate for enhancement of the lesions.
D. Carotid ultrasound – Evaluate for carotid stenosis.
E. MR angiogram of the head and neck – Evaluate for Moyamoya.

10. A 3-month-old, previously healthy baby girl is admitted with lethargy, poor feeding, and reduced bowel and bladder emptying. On exam, she is hypotonic and has a weak cry; dilated, sluggishly reactive pupils; and a poor suck and gag. Birth history is normal. Family medical history is unremarkable. She has no sick contacts. She is breastfed, and family endorses use of natural sweeteners on her gums to help with teething. What is the most likely diagnosis?
A. Central core disease
B. Nemaline rod myopathy
C. Infant botulism
D. Multi-minicore disease
E. Spinal muscular atrophy type II

Answers

1. E
2. A
3. E
4. C
5. D
6. C
7. A
8. B
9. E
10. C

Suggested Readings

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Sedation and Analgesia

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Contents

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Learning Objectives

- Emphasize the psychological and physiologic necessity of providing sedation and analgesia for patients in the PICU.
- Review the basic differences between a pediatric and adult airway and how they influence the assessment for sedation and pain control.
- Review the fundamental tenets of procedural sedation.
- Review the pharmacology, physiology, and rationale for use of the major sedative agents in the PICU.
- Review the pharmacology, physiology, and rationale for use of the major narcotic agents in the PICU.
- Discuss non-narcotic analgesics available for use in the PICU.
- Describe the risk factors and treatment for the development of opioid and benzodiazepine dependence, tolerance, and withdrawal.

27.1 Introduction

Significant pain and anxiety often accompany many forms of critical illness. The physiologic stress induced by pain and agitation can impede recovery and the delivery of critical care. Additionally, sedation of children may be required to maintain invasive devices often necessary for the monitoring and care of the critically ill or injured child. A thorough understanding of pain physiology and drug pharmacology is necessary to provide analgesia and anxiolysis.

Illness, injury, and environmental stimuli can result in a significant physiologic stress response. The increase in catecholamines and release of endogenous stress hormones may result in tachycardia, hypertension, hyperglycemia, and increased metabolic rate. In patients with pro-inflammatory states (i.e., sepsis, burns), the excessive release of inflammatory mediators may exacerbate ongoing multi-organ dysfunction.

Pain results in physiologic alterations that include liberation of stress hormones and augmentation of the systemic inflammatory response.

Using pharmacologic and nonpharmacologic measures to decrease the stress response may result in greater physiologic stability and facilitate recovery. Decreasing the effects of stress on critically ill patients has been shown to decrease morbidity and adverse events in the intensive care unit. Children who are inadequately sedated or experiencing pain may have preventable tachycardia, hypertension, and agitation. These children may be at increased risk for loss of vascular access, unplanned extubation, or self-injury. Conversely, oversedated patients are at risk for hemodynamic or respiratory compromise, prolonged mechanical ventilation, nosocomial infection, and critical illness myopathy. In addition, excessive sedation may impair the ability of providers to perform neurologic examinations. Prolonged sedation with narcotics or benzodiazepines may result in the development of tachyphylaxis, tolerance, and even dependence. Physiologic dependence may result in withdrawal symptoms upon drug cessation such as fever, diaphoresis, tachycardia, hypertension, and agitation. Children who develop dependence to sedative/opioids are at an increased risk of adverse drug side effects as the dosages necessary to achieve clinical effect continue to increase. Withdrawal impedes recovery by increasing metabolic rate and oxygen consumption. The pediatric provider must have an understanding of the appropriate use of pharmacologic and nonpharmacologic measures for each individual patient to achieve the optimal level of sedation and/or analgesia. Recent data suggests repeated or prolonged use of general anesthetic or sedation drugs in children younger than 3 years may have negative effects on their developing brains. Discussions should occur with parents and caregivers regarding the benefits, risks, timing, and duration of surgery or procedures requiring anesthetic and sedation drugs.

Providing procedural sedation for children outside the PICU has become common practice for pediatric intensivists.

Non-pharmacologic measures should be used to achieve anxiolysis and relaxation when appropriate. Use of relaxation techniques may reduce the total medication requirement and minimize the risks of cardiovascular and respiratory compromise. These techniques, often perfected by child life experts, are especially useful with planned procedural sedation, but can be successfully applied even in a busy intensive care unit. Creating a calm supportive environment (minimizing noise and bright lights) that incorporates familiar objects and parental involvement may decrease the need for pharmacologic intervention and minimize the incidence of delirium.

The choice of pharmacologic agent depends on many factors including the patient's age, physiologic stability, and underlying disease as well as the anticipated duration of sedation and/or analgesia. Children in the PICU may require prolonged administration (continuous or intermittent) of agents to allow ongoing relief of pain and anxiety and also to facilitate critical care therapies (i.e., mechanical ventilation). Additionally, intensivists are frequently called to provide sedation and analgesia to facilitate a procedure often referred to as procedural sedation. Procedural sedation for diagnostic and painful procedures is a growing area of practice within children's hospitals across the country.

27.2 Sedation: Analgesia Definitions and Scales

The level of sedation can be characterized using a descriptive spectrum that ranges from minimal sedation to general anesthesia. It is important that the provider have a predefined goal for the level of sedation and pain control prior to the administration of any drug. The term "conscious sedation" continues to be used despite its ambiguous and often inaccurate description of a sedated child. A child is either conscious and receiving medication to relieve anxiety or pain or sedated with an altered level of consciousness that may vary from easily arousable to complete obtundation. Table 27.1 provides uniform terminology for qualifying levels of sedation that is not specific to or limited by the

Table 27.1 Levels of sedation

	Minimal	Moderate	Deep	General anesthesia
Cognitive function	Normal to partially impaired	Partially to fully impaired	Fully impaired	Fully impaired
Responsiveness	Normal response to verbal commands	Purposeful response to verbal commands and/or light touch	Purposeful response to painful stimulation	No response to stimulation
Airway patency	Normal	May require intervention	Occasionally require intervention	Often require intervention
Spontaneous breathing	Normal	Normal to adequate	May be impaired	Often impaired
Cardiovascular function	Normal	Normal	May be impaired	Occasionally impaired

Adapted from the 2002 American Society of Anesthesiology Practice Guidelines

type or amount of drug administered. A child may quickly transition from one level of sedation to another without obvious clinical signs, and a previously stable airway may become impaired. The Joint Commission (formerly known as JCAHO – Joint Commission for Accreditation of Healthcare Organizations) states that this should be anticipated by the provider and he/she should be competent in managing a child at least one level of sedation deeper than intended. Medications used for sedation and analgesia can be classified based upon their main clinical effects (Table 27.2).

Physiologic markers may provide the most useful clinical information regarding depth of sedation and level of comfort.

Identifying and addressing the issues of pain and anxiety becomes more difficult in patients who are unable to communicate because of age or physical or mental disability. Additionally, subjective descriptions of level of sedation may vary widely among examiners. It may be more useful to follow physiologic markers such as tachycardia, hypertension, diaphoresis, and nonverbal response (i.e., facial expression) to stimuli in order to assess level of comfort. A recent survey designed to examine sedation management, sleep promotion, and delirium revealed a diverse practice style among providers. The lack of a formal scoring system was more common than any formalized process. In North America, the COMFORT Scale and State Behavioral Scale (SBS) were employed more commonly, while internationally, the COMFORT Scale and Ramsay Sedation Scale were more common. The COMFORT Scale was devised as a measurement of distress in ventilated critically ill children and utilizes five behavioral and three physiological parameters to assess level of sedation and pain control (Table 27.3). The SBS was developed to assess the

Table 27.2 Common definitions for terms related to sedation and analgesia in the PICU

Analgesic	Relieves pain by altering perception of nociceptive stimuli
Sedative	Decreases activity, moderates excitement, and calms the patient
Anxiolytic	Relieves apprehension and fear due to an anticipated act or illness
Amnestic	Affect memory incorporation such that the patient is unable to recall events after the delivery of drug
Hypnotic	Produces drowsiness and aids in the onset and maintenance of sleep

Table 27.3 COMFORT Scale

Characteristic	Evaluate	Points
Alertness	Deeply asleep	1
	Lightly asleep	2
	Drowsy	3
	Awake and alert	4
	Hyper-alert	5
Agitation	Calm	1
	Slightly anxious	2
	Anxious	3
	Very anxious	4
	Panicky	5

(continued)

Table 27.3 (continued)

Characteristic	Evaluate	Points
Respiratory response	No coughing	1
	Spontaneous respiration with little response to ventilation	2
	Occasional coughing with little resistance to the ventilator	3
	Active breathing against the ventilator	4
	Actively fighting the ventilator and coughing	5
Physical movements	None	1
	Occasional, slight movements	2
	Frequent, slight movements	3
	Vigorous movements of extremities only	4
	Vigorous movements of extremities, torso, and head	5
Blood pressure (mean)	Below baseline	1
	Normal	2
	Infrequent elevations of 15% or more above baseline	3
	Frequent elevations of 15% or more above baseline	4
	Sustained elevation of 15% or more above baseline	5
Heart rate	Below baseline	1
	Normal	2
	Infrequent elevations of 15% or more above baseline	3
	Frequent elevations of 15% or more above baseline	4
	Sustained elevation of 15% or more above baseline	5
Muscle tone	Relaxed/none	1
	Reduced muscle tone	2
	Normal muscle tone	3
	Increased tone/flexion – fingers/toes	4
	Extreme rigidity/flexion – fingers/toes	5
Facial tension	Facial muscle relaxed	1
	Normal tone	2
	Some tension	3
	Full facial tension	4
	Facial grimacing	5

Adapted from Ambuel et al. (1992)
Excessive sedation 8–16; adequate sedation 17–26; insufficient sedation 27–40

sedation-agitation continuum as it applies to intubated and ventilated infants and young children. The scale is based on a child's response to stimuli that would occur during normal nursing bedside care and is calculated by scoring that response within the context of seven dimensions, i.e., response to ventilation, cough, tolerance to care, etc. The COMFORT Scale has been validated in all ages and for differing levels of neurologic function. Using the total

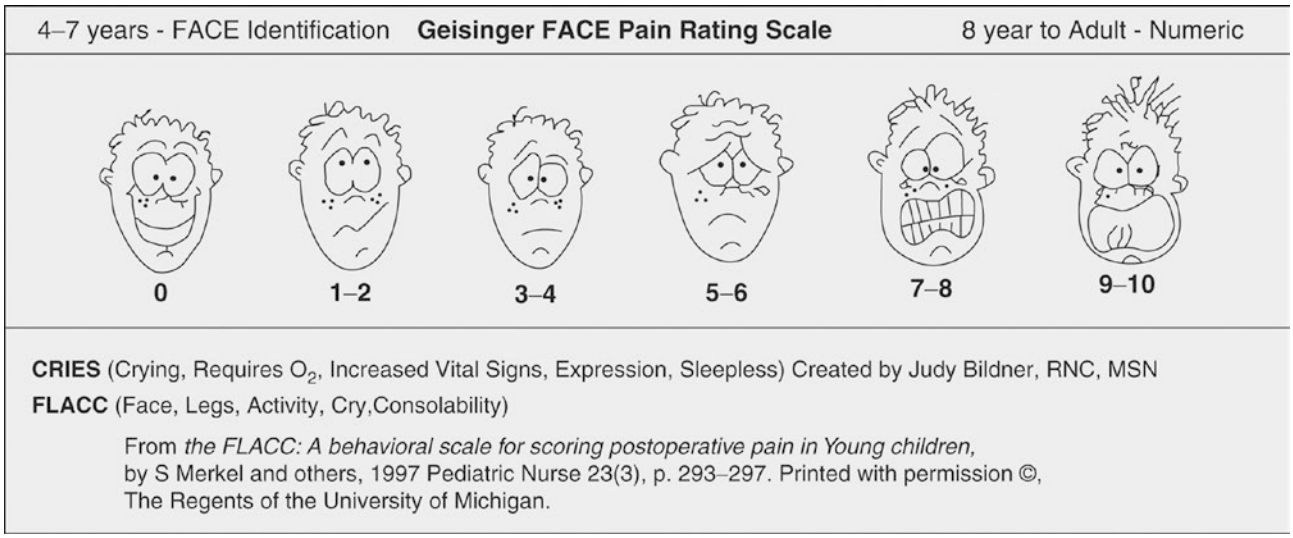


Fig. 27.1 A modified Wong-Baker Faces pain rating scale

COMFORT score can help quantify the level of sedation where 8–16 points indicates excessive sedation, 17–26 points indicates optimal sedation, and 27–40 points indicates inadequate sedation.

The Pediatric Sedation State Scale (PSSS) is a more recent scoring system that is applied to non-ventilated patients. In particular, this scale is used to assess effectiveness and quality of procedural sedation in children. Unlike previous sedation scales, this tool can allow comparison of a child's state of sedation whether they are receiving minimal or deep levels of sedation. Self-reported measures such as the Oucher scale or Wong-Baker scale utilize either a series of photographs of a young child's face or a vertical numeric scale (1–100 or 1–10) to represent varying levels of pain experienced by the child. Modifications of these scales are numerous and include a modified Wong-Baker Faces scale as noted in Fig. 27.1.

Objective measures of the effect of sedatives and anesthetics include electrophysiologic monitoring. A processed EEG, the Bispectral Index, has been evaluated for use in the PICU and may have some utility in patients with ongoing need for neuromuscular blockade. In these patients, chemical paralysis impedes the use of objective measures to clinically assess the level of sedation.

27.3 Pre-sedation Assessment for the Non-intubated Patient

27.3.1 History

A general history of each child should be known prior to administering sedative and analgesic medications. Important historical information that may impact the choice of medications administered is summarized in ▶ Box 27.1.

Box 27.1 Pre-sedation Assessment
- Active medical issues
- Current medications
- Known allergies
- Known adverse reactions to medications

- Previous history of sedation or anesthesia and any complications
- History of significant snoring or apnea
- Known anatomic limitations to opening mouth or moving head and neck
- Loose teeth or presence of dental devices
- Time since last oral or enteral intake
- Recent illnesses (fever, upper respiratory infection, etc.)
- Family history of problems with sedation or anesthesia

27.3.2 Physical Examination

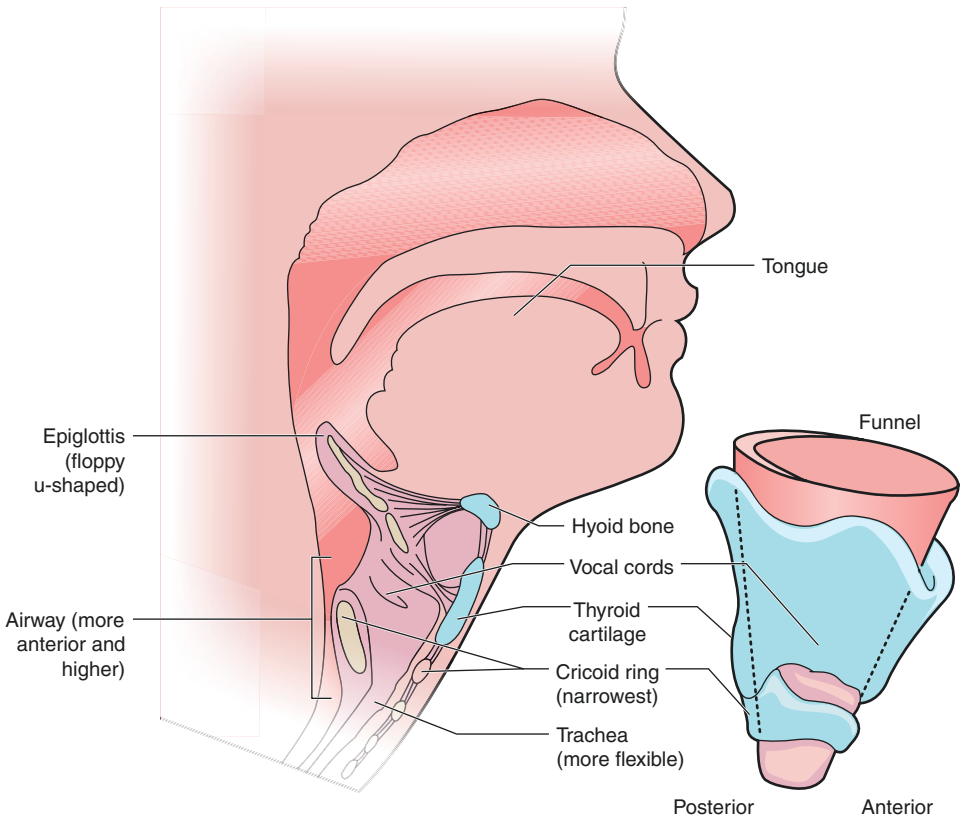
A focused pre-sedation assessment should be completed on all children receiving procedural sedation.

A child undergoing procedural sedation requires a focused pre-sedation examination which includes assessment of vital signs, cardiopulmonary function, and baseline neurological status. Among the most important components of the pre-sedation examination is the airway assessment.

An appreciation of the unique features of the pediatric airway allows the examiner to make an accurate pre-sedation assessment and provide advanced airway management if needed. The pediatric airway is anatomically different from that of an adult (see ◘ Fig. 27.2).

The pediatric airway has several anatomic differences (compared to an adult) that should be carefully considered during an assessment for sedation or endotracheal intubation.

A child's tongue is relatively larger compared to the space it occupies in the oropharynx. In a child with macroglossia, micrognathia, or retrognathia, the relative oral airway space is even more limited. The younger child's larynx is located more anterior and superior. Relative to the adult epiglottis, a child's is longer, more narrow, and more floppy. Children less than 8–10 years of age have the narrowest part of their upper airway located in the subglottic region



◘ **Fig. 27.2** Pediatric airway. (Adapted with permission by Susan Gilbert, Tunik et al. 2006)

at the level of the cricoid cartilage. Any obstruction at this level may significantly impair airflow. When supine, the large occiput of an infant can cause flexion at the neck, potentially causing partial or complete obstruction of the airway. This can be treated by placing a roll or towel under the shoulders and neck to create the desired "sniffing" position. In older children without the occiput prominence, a small pad or roll placed under the head can facilitate the desired position.

The Mallampati (MP) classification was first developed in the mid-1980s and was based on the ability to visualize the pharyngeal structures using a simple light source in a cooperative patient. While there were initially three grades of view, the current classification is based on four grades and is known as the Modified Mallampati. This tool has been used to predict difficult intubation based on visualization of pharyngeal structures. The sitting child is asked to open his/her mouth as wide as possible and stick out his/her tongue. No vocalization should be elicited. The pharyngeal structures are examined using a light source and classified based on extent of visualization (see Fig. 27.3): class I, soft palate, fauces, uvula, and pillars seen; class II, soft palate, fauces, and uvula seen; class III, soft palate and base of uvula seen; and class IV, soft palate not visible. A child with a MP score of III or IV may be at higher risk for a difficult intubation. A recent study of children found the MP score to be an independent predictor of obstructive sleep apnea. For every 1 point increase in the MP score, the odds ratio of having OSA increased by greater than sixfold. The MP classification, while routinely used during the pre-assessment for procedural sedation, has not been validated in children to predict difficult laryngoscopy. In fact, investigators using a national data warehouse for pediatric procedural sedation data found no difference in adverse events between children with a I/II score compared to those with III/IV scores.

After completing the history and physical exam, assignment of an American Society of Anesthesiologists (ASA) classification rank can be helpful in stratifying patients according to their relative risk of sedation. Although the classification was developed for risk stratification of patients undergoing general anesthesia, it has also been used for patients undergoing procedural sedation.

Although the classification was developed for risk stratification of patients undergoing general anesthesia, it has also been used for patients undergoing procedural sedation.

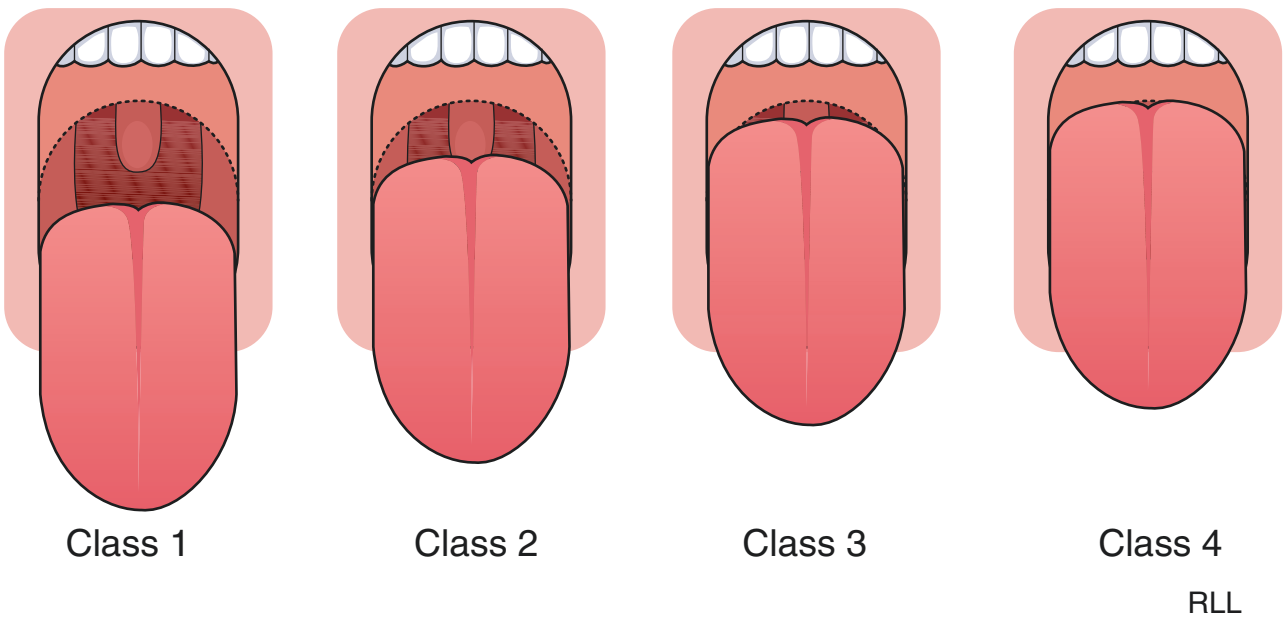


Fig. 27.3 Classification of pharyngeal structures. (Note that in class III the soft palate is visible but in class IV it is not)

Table 27.4 ASA Classification

ASA Classification	
ASA I	Normal healthy patients
ASA II	Patients with mild systemic disease
ASA III	Patients with severe systemic disease that is limiting but not incapacitating
ASA IV	Patients with incapacitating disease which is a constant threat to life
ASA V	Moribund patients not expected to live more than 24 h
ASA VI	A declared brain dead patient whose organs are being removed for donor purposes

tion. It is meant to provide a uniform method of assessing sedation risk. In general, ASA I and II are considered low risk, while ASA III and above are high risk and associated with more adverse respiratory events during sedation (Table 27.4).

27.3.3 Monitoring

All children undergoing the administration of sedation to facilitate invasive (e.g., endoscopy, lumbar puncture) or noninvasive procedures (e.g., neuroimaging) require continuous cardiopulmonary monitoring including pulse oximetry. While capnography is not required by Joint Commission standards or by American Academy of Pediatrics recommendations, it can be an invaluable tool in the monitoring of adequate airway patency and ventilation. This is particularly true in situations where the providers are physically separated from the patient and/or unable to visualize respiratory efforts (e.g., such as during MRI or radiation therapy procedure).

27.4 Sedative Medications

27.4.1 Benzodiazepines

27.4.1.1 Pharmacology

The chemical structure of the benzodiazepines (BNZ) contains a benzene ring fused to a diazepine ring, hence their name. Benzodiazepines produce their sedative effect by enhancing the activity of the CNS inhibitory neurotransmitter gamma aminobutyric acid (GABA). An appreciation of the GABA receptor complex is essential when considering the mechanism of action of a variety of sedative hypnotic drugs. The GABA receptor complex is a transmembrane chloride ion channel with specific drug binding sites (Fig. 27.4). Benzodiazepine binding in the cleft between the alpha and gamma subunit of the GABA receptor causes a conformational change in the receptor complex. This conformational change leads to a much higher affinity for the GABA neurotransmitter to bind the receptor complex. GABA binding leads to an intracellular chloride ion influx, hyperpolarization, and resistance to neurotransmission. Inhibition of neurotransmission produces sedative and anxiolytic effects. While GABA is the main inhibitory neurotransmitter in the brain, glycine is the major inhibitory neurotransmitter in the spinal cord and brain

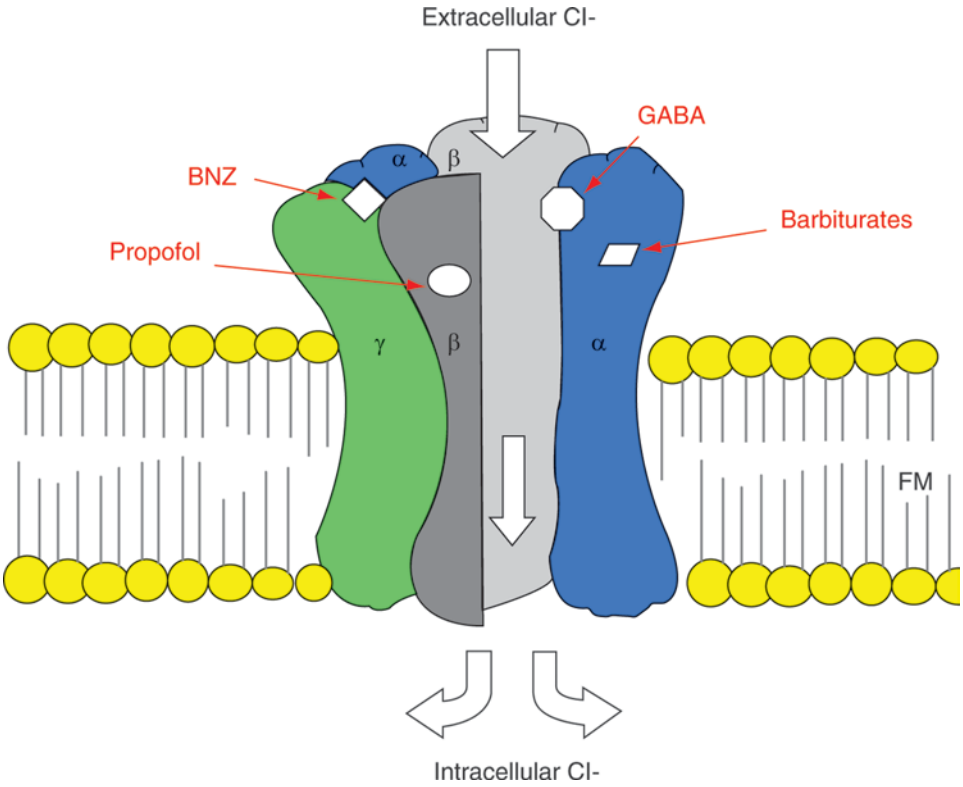


Fig. 27.4 GABA receptor complex demonstrating multiple drug binding sites. Drug binding potentiates GABA binding leading to increased chloride ion influx, hyperpolarization, and ultimately resistance to neurotransmission. Benzodiazepine binding occurs in the cleft between the alpha and gamma subunit

stem, and its activity is similarly augmented when the BNZ molecule binds to its receptors.

Most benzodiazepines are metabolized via the hepatic cytochrome P450 (CYP) isoenzyme complex. Up until the second month of life, the hepatic CYP system is immature, and its decreased activity may lead to prolonged effects of BNZ and opioids metabolized by this pathway.

Glycine is the major inhibitory neurotransmitter in the spinal cord and brain stem, and its activity is similarly augmented when the BNZ molecule binds to its receptors.

27.4.1.2 Clinical Effects

Benzodiazepines have sedative, hypnotic, amnestic, and anxiolytic properties. Alterations in consciousness are dose dependent. Low doses can provide anxiolysis without significant alterations in consciousness, whereas higher or cumulative doses result in deep sedation and possibly loss of protective airway reflexes and respiratory drive. Anterograde amnesia (amnesia after dosing) is also a well-known and appreciated clinical effect of BNZs. Retrograde memories are typically spared, though some degree of retrograde amnesia may be reported.

27.4.1.3 Clinical Indications

Indications for BNZ use include intermittent dosing to provide periodic anxiolysis or alternatively as a continuous infusion to provide ongoing sedation. Benzodiazepines do not provide pain relief; an analgesic should be administered to the child requiring sedation *and* pain control.

27.4.1.4 Adverse Effects

The CNS response to hypercarbia as well as to hypoxia is blunted by BNZs. Therefore, in the non-intubated patient, caution should be used with higher dosing to prevent drug-induced respiratory depression. Administration of BNZs in patients on mechanical ventilation may require augmentation of minute ventilation. Central respiratory depression is further increased by the co-

administration of opioids, a common practice during both procedural and continuous sedation.

Benzodiazepines cause a decrease in SVR leading to a reduction in preload and afterload with minimal changes in cardiac output.

Benzodiazepines decrease sympathetic outflow resulting in several hemodynamic changes. A reduction in systemic vascular resistance causes reduction in both preload and afterload, while cardiac output and resultant arterial blood pressure are usually unaffected. Hemodynamic compromise is uncommon except in children who have concomitant cardiovascular disease as can be seen with septic shock and hypovolemia and in postoperative congenital heart repair. These situations are not absolute contraindications to the administration of a BNZ, but lower initial doses should be used.

Benzodiazepines also carry a risk of toxicity due to pharmaceutical excipients. Excipients are inactive compounds that are added to the active drug as a preservative or to facilitate drug delivery. Diazepam and lorazepam utilize propylene glycol (PG), in varying concentrations, as a solvent. As much as 40%, per volume, of IV diazepam is solvent. While deemed safe as a vehicle for drug administration by the US Food and Drug Administration, there are reports of toxicity including death. The mechanism by which it causes toxicity is unclear. Metabolites of PG include pyruvate, acetate, and lactate, but evidence is lacking to directly implicate these metabolites as the cause of clinical toxicity.

Propylene glycol is a preservative used in lorazepam and diazepam. Benzyl alcohol is a preservative used in lorazepam, diazepam, and midazolam. Accumulation of these excipients can cause fatal toxicity.

Benzyl alcohol (BA) is a preservative that is found in diazepam, midazolam, and lorazepam. There are preservative-free preparations of midazolam available for use. Benzyl alcohol toxicity has been reported in neonates, particularly those born less than 36 weeks of gestation. Like PG, the mechanism of BA-related toxicity is poorly understood. Clinical signs and symptoms for both excipient toxicities are similar and include new-onset acidosis, hyperosmolality, and hemodynamic instability. Benzyl alcohol toxicity may include the unique finding of "gasping" respirations in neonates. Recommendations to prevent the development of severe PG or BA toxicity include monitoring for acidosis, hyperosmolality, cardiac arrhythmias, seizures, and hemodynamic instability, especially in small infants on continuous infusions. For children receiving higher than normal rates of infusion, i.e., control of refractory seizures, the FDA recommends limiting BA dosage to less than 99 mg/kg/day.

27.4.2 Midazolam

Midazolam (Versed) is an imidazobenzodiazepine that has rapid onset, short duration, water solubility and is commonly used for both procedural sedation and continuous IV infusion in critically ill children. It may be given via oral, sublingual, nasal, rectal, IM or IV routes. Its water soluble properties decrease incidence of thrombophlebitis or discomfort on injection. Shortly after parenteral administration, a change in ring structure from open to closed occurs due to its exposure to physiologic pH ~ 7.4. This closure of the ring increases its lipid solubility allowing rapid entrance into the CNS. This accounts for the drug's rapid onset. Metabolism occurs via the hepatic CYP 450 system, in particular P450-3A4. Midazolam levels may be altered by drugs that induce or inhibit the P450-3A4 enzyme complex, i.e., erythromycin, itraconazole and diltiazem to name a few. 1-Hydroxymidazolam is an active metabolite equipotent to the parent drug. This active metabolite is renally excreted and therefore may accumulate in children with renal insufficiency. In children with liver failure, not only will metabolism of the parent drug be decreased, protein binding of the free drug may be decreased as well, leading to increased drug effects. Similar increased fraction of free drug can be seen in patients on heparin, as it displaces midazolam from protein binding sites.

The most common route of administration in the PICU is intravenous boluses either alone as an anxiolytic or to supplement a continuous infusion in ventilated patients. The recommended bolus dose is 0.025–0.1 mg/kg per dose. The dose range for continuous infusion is 0.05–0.2 mg/kg/h. Larger doses may be needed to achieve adequate sedation for the ventilated child. While increasing the infusion rate, it may be necessary to increase prn doses as well to maintain the desired sedative effect. Treatment of refractory status epilepticus may require dosing as high as 1 mg/kg/hr.

27.4.3 Diazepam

The use of diazepam (Valium) in the PICU has generally been replaced by midazolam and lorazepam. It has a rapid onset of action due to its inherent lipophilic properties. Its duration of action (1–2 h), on the other hand, is closer to that of lorazepam. It may be administered via oral, rectal, and IV routes. Intravenous administration can produce pain upon injection and thrombophlebitis due to its high osmolality and lipophilic nature. It is metabolized in the liver by N-demethylation into the active metabolites oxazepam and nordazepam. Subsequent metabolism of these active compounds is longer than the parent compound and thus contributes to the long duration of action. Due to the presence of these active metabolites, frequent repeated dosing and continuous infusions of diazepam are not recommended.

27.4.4 Lorazepam

Lorazepam (Ativan), like midazolam, is a water-soluble BNZ that is frequently used in critical care. It is metabolized via hepatic phase II glucuronidation and not by CYP 450 phase I reactions. Since lorazepam does not undergo phase I CYP 450 reactions, its potential for drug-drug interactions is less than midazolam. Lorazepam can be administered in children with mild to moderate liver dysfunction since phase II reactions are often preserved until end-stage disease. Lorazepam can be used in patients with renal insufficiency since no active metabolite requires renal clearance.

Lorazepam is metabolized by glucuronyl transferase and does not have active metabolites, making it a potentially safer choice in patients with liver or kidney dysfunction.

Lorazepam can be administered enterally, IM, or intravenously. Intravenous lorazepam has a 2–5 min onset of action and its duration is generally 3–6 h. The enteral route has a longer onset of action (15–30 min) but a similar duration of action.

Intermittent IV dosing and continuous infusions are common methods for administering lorazepam in the PICU. Intermittent doses of 0.05–0.1 mg/kg every 2–4 h are used in children on mechanical ventilation who require ongoing sedation. Continuous infusions of lorazepam can be started at 0.025–0.05 mg/kg/h and titrated as needed while carefully monitoring for adverse effects, especially those created by the accumulation of propylene glycol. Intermittent enteral or IV lorazepam can be initiated in patients on continuous benzodiazepine infusions to allow easier weaning from intravenous administration.

27.4.5 Benzodiazepine Antagonist

Flumazenil, a GABA receptor antagonist, competitively inhibits the activity at the BNZ recognition site on the GABA receptor complex. This leads to a reversal of the clinical effects of BNZs. This may be particularly useful in the

Flumazenil administration may cause seizures in patients that have been on long-term benzodiazepine therapy.

setting of an acute overdose. The half-life of flumazenil is shorter than any of the commonly used BNZs; thus, re-dosing of flumazenil may be necessary to avoid return of overdose symptoms such as respiratory depression. In children and adults, seizures have been reported after flumazenil administration. However, this has generally occurred in patients with co-ingestions (e.g., tricyclic antidepressants) or in patients on long-term BNZ therapy.

27.4.6 Non-benzodiazepine Sedatives

27.4.6.1 Propofol

Pharmacology

Propofol is an IV general anesthetic of the alkylphenol family that is unrelated to other general anesthetics or routinely used sedative medications. Pharmaceutical excipients include 10% soybean oil and 1.2% egg phosphatide. Propofol's mechanism of action is not completely understood but is thought to decrease the rate of dissociation of GABA from its receptor, thereby increasing the duration of the GABA activated opening of the chloride channel and subsequent hyperpolarization.

Propofol has high lipid solubility, large volume of distribution, and a rapid metabolic clearance. It has a rapid onset and a short recovery time. The pharmacokinetics of propofol are best described using a three-compartment model. Following IV administration into the central vascular compartment, propofol rapidly distributes into the CNS (second compartment) and produces its clinical effects. Propofol also distributes into a third compartment considered to be the peripheral tissues. This third compartment may become saturated during prolonged infusions resulting in a significantly decreased volume of distribution. Therefore, during prolonged infusions, dosing should be titrated down to the minimal dose required to produce adequate sedation, thus reducing the potential for adverse effects. Propofol undergoes rapid hepatic metabolism mainly via glucuronidation with minimal contribution from the CYP pathway. Extrahepatic metabolism in the lungs, kidneys, brain, and small intestine via glucuronidation accounts for as much as 40%. In the operating suite, propofol is one of the most common agents utilized for induction and endotracheal intubation. Induction doses range from 1 to 3 mg/kg.

When used for procedural sedation, boluses of 0.5–1 mg/kg are typically given until a level of moderate to deep sedation is obtained. Sedation can be maintained using infusions ranging from 50 to 200 mcg/kg/min. Infants have a larger volume of distribution and as such may require increased dosing compared to older children.

Clinical Effects

Propofol provides sedative, hypnotic, and amnestic effects but does not have analgesic properties. Respiratory depression is dose dependent and likely mediated by a decrease in the normal physiologic response to hypercarbia. Tidal volumes are decreased, while respiratory rate is usually maintained or increased to achieve normal minute ventilation. Propofol lowers peripheral vascular resistance via endogenous nitric oxide release and calcium channel blockade. Negative inotropy directly related to propofol continues to be debated. Propofol causes a decreased calcium uptake into the sarcoplasmic reticulum. However, this does not typically lead to a decrease in myocontractility at clinical concentrations. Increases in myofilament sensitivity to activated calcium are thought to be responsible for this effect. Nonetheless, lower systolic and diastolic blood pressure are usually noted in the child being administered propofol. If the child

becomes hypotensive, a decrease in dosing and a bolus of isotonic fluid will typically correct the decrease in blood pressure. Reflex tachycardia after initial dosing is not uncommon. Propofol has antiemetic and anticonvulsant properties. Propofol lowers intracranial pressure as well as cerebral metabolic rate.

Clinical Indications

Propofol remains not approved for continuous sedation in the pediatric intensive care unit setting. However, many PICUs use short-term infusions without apparent harm.

Propofol is commonly used for procedural sedation because of its favorable pharmacologic profile. Its rapid onset and rapid metabolism make it an ideal sedative for brief non-painful procedures. If used for painful procedures, an opioid should be added to provide analgesia. Propofol is commonly used for continuous sedation in adult ICU patients, in particular those with traumatic brain injury. In response to the reports of propofol infusions syndrome (see below) in children and citing a randomized study showing increased mortality with the use of propofol in the PICU, the FDA first published in 2001, and repeated in 2017, a warning against the use of propofol for continuous sedation in the pediatric intensive care unit. However, many PICUs use short-term (hours) infusion for sedation in the PICU without apparent harm.

Adverse Effects

Propofol causes dose-dependent respiratory depression via decreased inspired tidal volumes and a higher threshold for serum carbon dioxide levels.

High doses of propofol can produce apnea, and therefore, clinicians administering the drug should be capable of maintaining airway patency and gas exchange. Cough and gag reflexes are intact but are often diminished.

In healthy children, mild hypotension is common but rarely clinically significant. However, in children with preexisting cardiovascular compromise, propofol can produce hemodynamic instability.

Intravenous administration may produce immediate and delayed pain at the injection site, particularly when administered into smaller veins. The etiology of the pain is unclear but thought to be related to the lipid portion of propofol activating the plasma kallikrein-kinin system as well as its non-physiologic pH (7.5–8.0). To counteract the discomfort, lidocaine can be mixed with the propofol solution or injected in a small aliquot (1 mL of 10 mg/mL concentration) into the vein and allowed to dwell for 1 min prior to administering the propofol. A tourniquet should be applied above the IV site during the dwell time to increase local venous anesthetic effect. The tourniquet is removed after the 1 min dwell, and initiation of infusion or boluses can then occur. Care must be taken to avoid propofol extravasation. Case reports of skin and subcutaneous infiltrations range from minor skin irritation to development of severe full thickness necrosis and loss of tissue. Hypertriglyceridemia from the high lipid content (10% lipid) may also occur.

Refractory metabolic acidosis and cardiovascular collapse related to propofol infusions were first noted in the early 1990s. Additional cases led to the elucidation of propofol infusion syndrome (PRIS). The syndrome is characterized by lactic acidosis, rhabdomyolysis, arrhythmias (particularly pharmacologically refractory bradycardia), myocardial failure, renal failure, hyperlipidemia, and hepatomegaly. Fatalities due to PRIS are reported as high as 60%. Propofol infusion syndrome is often associated with high doses (>70 mcg/kg/min or 4 mg/kg/h) and/or long-term (>48 h) infusions. Evidence suggests that propofol may trigger dysfunction at the mitochondrial level, leading to depletion of ATP and cellular hypoxia. Postmortem evaluation and muscle biopsies of PRIS patients demonstrate abnormalities reminiscent of congenital mitochondrial disease and disorders of fatty acid oxidation. These findings and the sporadic nature of PRIS suggest that there may be an inherent congenital susceptibility to developing PRIS. Additionally, it is thought that a variety of critical illnesses and medications (i.e., glucocorticoids) can "prime"

the respiratory chain to become susceptible to propofol-triggered mitochondrial dysfunction. Treatment is withdrawal of drug, supportive care, and hemodialysis or plasmapheresis in refractory cases. Temporary cardiac pacing may be required for severe bradycardia. In patients on continuous propofol infusions, serial measurement of lactate, HCO3, and triglycerides may provide for early detection of PRIS.

Allergic reactions to propofol have been reported in children with severe egg, soy, or peanut allergy. Although recent data has called this association into question, propofol should still be used with caution in this patient population.

27.4.7 Ketamine

27.4.7.1 Pharmacology

Norketamine and hydroxynorketamine are active metabolites of ketamine and may accumulate in children with hepatic dysfunction.

Ketamine is a phencyclidine (PCP) derivative that produces its effects by noncompetitively blocking central N-methyl (NMDA) receptors, leading to inhibition of glutamate-mediated neurotransmission. It undergoes hepatic N-methylation to two active metabolites, norketamine and hydroxynorketamine. Norketamine has approximately 25–33% the potency of the parent drug and inhibits NMDA receptors. Hydroxynorketamine has a role in upregulating AMPA receptors and has been shown to be effective as a potent antidepressant. Both active metabolites undergo further hepatic metabolism to inactive molecules that are renally excreted. Children with hepatic dysfunction should have doses decreased and titrated to effect.

Ketamine can be given via enteral, nasal, rectal, IM, and IV routes. Ketamine dosing for procedural sedation is typically 1–2 mg/kg IV and 2–4 mg/kg IM. Continuous infusion dosing ranges from 0.5 to 2 mg/kg/h.

27.4.7.2 Clinical Effects

Ketamine produces dose-dependent sedative, amnestic, and analgesic effects. At lower doses, ketamine primarily causes analgesia and anxiolysis, whereas sedation is achieved at higher doses. It is not uncommon for a child receiving ketamine to achieve a moderate level of sedation and still have his/her eyes open. Ketamine is a potent analgesic. Ketamine is well tolerated and has a long-standing safety record. Spontaneous respirations and airway tone are usually maintained. Ketamine causes an increase in catecholamine release as well as cholinergic receptor stimulation producing bronchodilation.

27.4.7.3 Clinical Indications

Ketamine has been used for a variety of purposes including induction for general anesthesia, perioperative analgesia, and procedural sedation. Its potent analgesic effects make it an excellent choice for children undergoing painful procedures such as fracture reduction. Due to its ability to produce bronchodilation, ketamine infusions for sedation may be of particular benefit in the critically ill asthmatic child.

27.4.7.4 Adverse Effects

Salivary and tracheobronchial mucous gland secretions may increase and can be treated with antisialogogues such as glycopyrrolate or atropine. Increased laryngeal sensitivity may also occur which can lead to laryngospasm.

Ketamine has direct negative inotropic effects. However, these effects are usually counteracted by its indirect sympathomimetic activity. Heart rate and cardiac output are typically increased. In patients with poor cardiac function, hypovolemia, or diminished endogenous catecholamine reserves, ketamine may

produce hemodynamic instability. In adults, studies have shown increases in pulmonary vascular resistance (PVR), whereas data in children is less clear. In patients with known pulmonary hypertension, ketamine should be used with caution.

Emergence reactions can occur when a child is awakening and may present as hallucinations, confusion, or agitation. Benzodiazepines may help minimize this response and can be given in small doses that will not lead to over-sedation. It remains unclear whether the BNZ dose should be given prior to or after ketamine to be most effective. Historically, ketamine was associated with causing an increase in intracranial pressure (ICP) due to proposed cerebral vasculature vasodilation, increased blood flow, and increased cerebral metabolism. However, recent adult data has not demonstrated increased ICP or changes in cerebral perfusion pressure (CPP) after ketamine administration. In a prospective study of 30 ventilated children with severe traumatic brain injury, ketamine administration in well-sedated children was associated with a statistically significant decrease in ICP and statistically significant increase in cerebral perfusion pressure. While lower ICPs are desired in children with traumatic brain injury, an excessive increase in CPP may not be advantageous. This data suggests the need for continued investigations regarding the safety of ketamine use in children with increased ICP.

Ongoing research is needed to clarify ketamine's role in sedation and analgesia in pediatric traumatic brain injury.

27.4.8 Barbiturates

27.4.8.1 Pharmacology

Barbiturates exert their sedative hypnotic effects by several mechanisms. At low doses, barbiturate binding to the GABA receptor enhances inhibitory neurotransmission. At high doses, like those used for anesthesia and pharmacologic coma, barbiturates cause direct cell hyperpolarization independent of GABA receptor binding. Lastly, barbiturates may also inhibit synaptic transmission of excitatory neurotransmitters, such as glutamate and acetylcholine. The barbiturates are typically classified into ultra-short-, medium-, and long-acting agents based on their individual pharmacology. Metabolism occurs via hepatic conjugation and oxidation into inactive metabolites that are renally excreted.

27.4.8.2 Clinical Effects

Barbiturates have dose-dependent sedative and hypnotic effects. It is important to note that barbiturates do not produce analgesia and indeed when given in small doses may cause a paroxysmal increase in the perception of pain. Excitement or agitation may accompany this phenomenon. At higher doses, sedation is achieved, but pain perception remains. Further dosing will lead to general anesthesia and loss of pain perception. Barbiturates are potent anticonvulsants and can reduce cerebral blood flow and metabolism.

27.4.8.3 Clinical Indications

Barbiturates have become less commonly used agents for sedation, supplanted by the continued safety of benzodiazepines and the increased familiarity and success of propofol and dexmedetomidine. Continuous barbiturate infusions are typically reserved for the treatment of refractory status epilepticus or intracranial hypertension.

Pentobarbital (Nembutal) is a medium-acting agent with an onset of action of 1–5 min and peak effect at 10 min. It has a relatively long duration of action and typically lasts 2–6 h. It may be given via enteral, IM, or IV routes. Continuous infusions are generally reserved for patients who require cerebral

coma as treatment for refractory seizures or in patients with refractory elevated ICP. Pentobarbital causes a decrease in cerebral blood flow and cerebral metabolism, leading to lower ICP. Typical starting dose for continuous infusion is 1 mg/kg/h and is titrated to effect. Isoelectric activity is usually achieved at doses between 4 and 6 mg/kg/h. Loading doses of 1–10 mg/kg (5 mg/kg most common) are given over 10–30 min prior to initiation of the infusion and intermittently thereafter until clinical effect is achieved.

Phenobarbital continues to be an important anticonvulsant, especially in infants. It is a long-acting barbiturate, and when given in IV form as a bolus, typical doses range from 10 to 20 mg/kg. It is well tolerated as an enteral medication in children with chronic seizure disorders.

Thiopental (Pentothal) and methohexital (Brevital) are short-acting barbiturates administered in IV bolus form in doses of 4–7 mg/kg and 1–2 mg/kg, respectively. Thiopental has a rapid onset of action making it an attractive agent for rapid sequence intubation. Thiopental and methohexital are rapidly distributed from the brain into other body compartments, resulting in a limited duration of activity.

27.4.8.4 Adverse Effects

Respiratory depression is dose dependent. Barbiturates have historically been described as direct negative inotropes. They also cause arterial vasodilation. The original study that examined barbiturate effect on myocardial contractility was done in 1969 on ex vivo tissue samples. Subsequent human data in the 1970s and 1980s did not find direct myocardial depression after barbiturate (thiopental) administration. These authors are not aware of any other human studies that corroborate direct myocardial depression. Nonetheless, there remains a general consensus in the literature that myocardial depression may occur in patients receiving barbiturate therapy. Reflex tachycardia and an increase in sympathetic mediated SVR act to maintain cardiac output and blood pressure. In children with preexisting cardiovascular compromise, barbiturate administration may lead to acute and profound hemodynamic instability. The mechanisms for this effect are not well understood. Thiopental, in particular, may cause bronchospasm.

Barbiturate-induced immunosuppression in critically ill children may lead to increased incidence of hospital-acquired infections.

Immunosuppression may occur in patients who have received multiple doses or are on a continuous infusion. The cause of immunosuppression is multifactorial and includes lymphocyte apoptosis, T cell dysregulation and inhibition of the enzyme activity of the calcineurin complex. Patients on barbiturates for continuous sedation are at increased risk for developing hospital-acquired infections such as ventilator-associated pneumonia, tracheitis, catheter-related infections, and sepsis. In patients receiving routine dosing of barbiturates, it is recommended to follow and maintain therapeutically appropriate serum levels.

27.4.9 Alpha 2 Adrenergic Agonists

Agonist binding of α_2 receptor subtypes produces varied clinical responses. Agonism to peripheral postsynaptic α_2 receptors on blood vessels produces vasoconstriction, whereas binding of central presynaptic α_2 receptors in the brain stem and spinal cord produces sympatholytic (vasodilation), sedative, and analgesic effects. Receptor binding in the locus coeruleus triggers a negative feedback mechanism that decreases neuronal norepinephrine production (Fig. 27.5). This ultimately leads to a decrease in sympathetic outflow and subsequent increase in inhibitory GABA activity. Binding of α_2 receptors in the dorsal horn of the spinal cord decreases the release of the neurotransmitter substance P and produces analgesia.

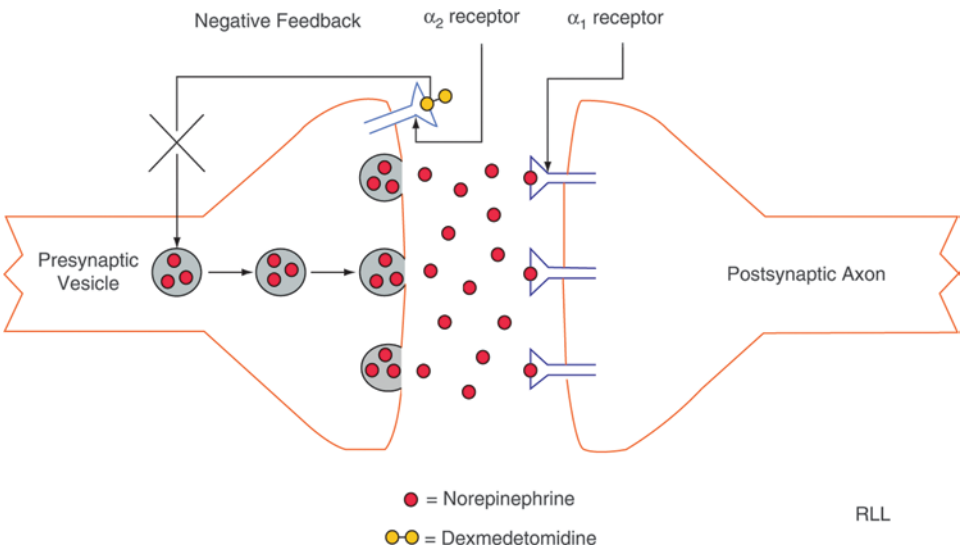


Fig. 27.5 Presynaptic binding of dexmedetomidine to the presynaptic α_2 receptor in the locus coeruleus initiates a negative feedback loop that leads to the inhibition of norepinephrine release into the synapse

27.4.10 Clonidine

Clonidine is a centrally acting α_2 agonist that selectively binds α_2:α_1 receptors in a 200:1 ratio. Often used enterally, its onset of action is 20–30 min and may last more than 90 min. Epidural injection will provide a peak effect approximately 15 min after administration. It has been used as a preanesthetic to reduce anxiety and induce light sedation but is rarely used for procedural sedation. In the PICU, a postoperative patient may be treated with an epidural containing clonidine with or without local anesthetics to maintain regional analgesia.

Clonidine is an effective antihypertensive agent. Its specificity toward central presynaptic alpha 2 receptors in the brain stem has a sympatholytic effect, suppressing NE release, ATP, renin, and neuropeptide Y, leading to a decrease in peripheral vascular resistance. Recent evidence also suggests that clonidine binds to imidazoline receptors in the medulla with a much greater affinity than α_2 receptors. Binding of the imidazoline receptors may be an additional central mechanism by which clonidine decreases blood pressure.

Clonidine is also effective as a non-opioid alternative for managing opioid withdrawal and as an adjunct therapy to opioids for neonatal abstinence syndrome.

27.4.11 Dexmedetomidine

27.4.11.1 Pharmacology

Dexmedetomidine is a potent α_2 receptor agonist that has shown extensive utility in treating pain, providing sedation, and moderating drug withdrawal.

Dexmedetomidine (Precedex) is an extremely potent α_2 receptor agonist that has eight times greater specificity for central α_2 receptors than clonidine (1600:1 vs. 200:1). Similar to clonidine, dexmedetomidine binds presynaptic α_2 receptors within the brain stem and spinal cord, triggering a sympatholytic cascade resulting in sedation and analgesia. Evidence also suggests that supraspinal α_2 binding by dexmedetomidine provides further analgesia.

Metabolism occurs via hepatic phase I CYP 450 oxidation and phase II glucuronidation to inactive metabolites. It should be used with caution and at lower dosing in patient with liver dysfunction. No dosing adjustment is required with renal impairment.

27.4.11.2 Clinical Effects

Dexmedetomidine produces sedation and analgesia in a dose-dependent fashion. It has minimal respiratory depressant effects. Cardiovascular effects are minimal and are due to centrally mediated sympathetic withdrawal and include bradycardia and peripheral vasodilation.

27.4.11.3 Clinical Indications

While not FDA approved for long-term sedation in children, dexmedetomidine has been used both as a sole agent and in conjunction with other sedative or narcotic agents to provide ongoing sedation and analgesia in the PICU. A recent RCT in adolescents receiving postoperative sedation revealed less fentanyl use, less delirium, and better quality of pain relief in the study group receiving dexmedetomidine infusion compared to the control group receiving midazolam. These findings are likely, in part, a result of the analgesic properties from centrally acting α_2 agonist. This agent is also becoming more widely used in cardiac ICUs and is often coupled with remifentanil infusions while the child is on mechanical ventilation. The lack of significant respiratory depressant effects allows dexmedetomidine to be used safely as a transitional sedative during the extubation process. It is also safely used in the non-intubated patient.

Dexmedetomidine has a favorable hemodynamic profile and has been used successfully in children following congenital heart repair. The recommended starting dose is 0.5–1 mcg/kg bolus followed by continuous infusion of 0.2–1.0 mcg/kg/h. The bolus must be given slowly over 10–20 min to minimize potentially life-threatening bradycardia. Dexmedetomidine may facilitate withdrawal from long-term use of opioids and benzodiazepines (see Sect. ► 27.7). Dexmedetomidine was first used as an agent for procedural sedation in 2005. In addition, intranasal administration at doses of 2–4 mcg/kg have been shown to be effective for non-painful procedures such as imaging. Onset is generally 10–15 minutes from intranasal administration.

27.4.11.4 Adverse Effects

Severe bradycardia can occur during rapid infusion of dexmedetomidine. Bolus injection should be given slowly over at least 10 min.

Centrally mediated sympathetic withdrawal can lead to parasympathetic dominance and augmented vagal activity which can lead to dose-dependent bradycardia. Bradycardia is usually more rapid and severe after a bolus. Children receiving a continuous infusion typically develop bradycardia in a slower, more insidious manner. Bradycardia may become clinically significant and may require a reduction in dosing or discontinuation. Resolution of bradycardia occurs quickly after discontinuation of the drug. Dexmedetomidine-induced bradycardia may be potentiated with concomitant use of other negative chronotropes such as digoxin.

27.4.12 Chloral Hydrate

Trichloroethanol, a metabolite of chloral hydrate, can accumulate in patients with renal or hepatic dysfunction and may cause cardiac arrhythmias.

Once a commonly used sedative, chloral hydrate has fallen out of favor in lieu of safer and more predictable sedatives. It is a sedative-hypnotic agent without analgesic properties. The mechanism of action is poorly understood but thought to involve the GABA receptor complex. It is metabolized in the liver to its active compound, trichloroethanol. It is administered enterally or rectally. Onset of action is approximately 20–30 min. The half-life is variable, ranging from 8 to 12 h in children and up to 40 h in young infants. Repeated dosing may lead to accumulation of active metabolites, especially in patients with hepatic or renal dysfunction. Trichloroethanol has been associated with ventricular arrhythmias, particularly in patients on tricyclic antidepressants.

Respiratory and cardiovascular compromise can occur with high initial dosing or with repetitive dosing; therefore, cardiorespiratory monitoring including pulse oximetry is required during chloral hydrate use. Nausea and vomiting may also occur. Due to its unpredictable pharmacokinetics, metabolites, and high failure rate, it has limited clinical utility (◘ Table 27.5).

27.5 Analgesic Medications

27.5.1 Opioid Analgesics

27.5.1.1 Pharmacology

Opioids are a group of drugs that are typically classified based on their chemical structure. Chemical structure classification: morphine-related drugs including morphine and hydromorphone; meperidine-related drugs including meperidine, fentanyl, and remifentanil; and diphenylheptanes that include methadone. Opioids can also be classified as naturally occurring opiates (codeine, morphine), semisynthetic opiates (heroin, hydromorphone), and synthetic opiates (methadone, fentanyl, remifentanil). Opioids produce opium-like effects by binding specific receptors in the brain, spinal cord, and peripheral tissues. Several opiate receptors have been identified in the central nervous system and include μ (mu), δ (delta), and κ (kappa). Receptor binding causes cell hyperpolarization, inhibition of neurotransmitter release, and ultimately decreased excitatory neurotransmission. Neurotransmitters that are inhibited include the excitatory neurotransmitter substance P. The opioids most commonly used in the management of pain are μ agonists. Receptor μ_1 binding produces analgesia and μ_2 binding produces analgesia and respiratory depression. All further references to μ receptors can be assumed to be μ_1 receptors. Miosis and euphoria may also occur as a result of μ receptor agonist activity. Metabolism of opioids is mainly hepatic, undergoing phase 1 metabolism via CYP450 isoenzymes 3A4, 2B6, and 2D6 or phase 2 metabolism via glucuronidation.

27.5.1.2 Clinical Effects and Indications

Opioids produce dose-dependent analgesia and remain the mainstay of therapy to alleviate severe pain in pediatric patients. The onset and duration of effect are dependent on the route and class of opioid used. In addition to analgesia, opioids possess sedative properties. Anxiolysis or euphoria may occur with low doses, whereas sedation typically occurs at higher doses.

Recent advances in genomics allow us to test patients to determine what type of response they will have to a certain drug. Similarly, a patient's genetic diversity can also indicate whether or not he or she is at increased risk for an adverse effect from the same drug. This field of study is known as pharmacogenetics, and while relatively new, it has great potential to personalize medicine and bring more dosing-related precision to the bedside clinician. Current literature classifies patients according to their ability to metabolize medication as follows, in order of decreasing gene activity: ultra-rapid, rapid, normal, intermediate, and poor metabolizers. The genetic polymorphisms, when better understood and universally available to the prescribing provider, will allow care that is safer and uniquely tailored to each individual patient.

27.5.1.3 Adverse Effects

Respiratory depression can occur even with low doses of opioids. Higher doses can cause apnea, particularly in neonates, given their immature CYP metabolism. Bradycardia and hypotension can occur but are usually minimal

Table 27.5 Sedative medications[a]

Drug	Dose	Infusion	Onset	Duration	Comments
Midazolam	0.05–0.1 mg/kg	0.05–0.2 mg/kg/h	0.5–1 min	30–60 min	Used commonly as continuous infusion
					P450 metabolism
Diazepam	0.05–0.1 mg/kg	0.05–0.1 mg/kg/h	0.5–1 min	1–2 h	Rapid onset due to high lipid solubility
					Heparin increases free fraction of drug
					Contains propylene glycol and sodium benzoate
Lorazepam	0.025–0.05 mg/kg	0.025–0.2 mg/kg/h	2–3 min	2–4 h	Slower onset due to low lipid solubility
					Metabolized via glucuronyl transferase and can be used in patients with mild liver dysfunction
					Contains propylene glycol
Propofol	1–3 mg/kg	25–200 mcg/kg/min	0.5–1 min	5–10 min	Rapid onset due to high lipid solubility
					Not approved for long-term use in the PICU
					May cause lethal propofol infusion syndrome
Ketamine	0.5–2 mg/kg	1–2 mg/kg/h	1–2 min	15–30 min	May cause tachycardia and hypertension
					Catecholamine-depleted patient can experience hypotension
					Bronchodilation and increased airway secretions
Pentobarbital	2–6 mg/kg	1–4 mg/kg/h	1–5 min	2–6 h	Potential negative inotropic effects
					Induced coma for refractory seizures
Clonidine	3–5 mcg/kg	N/A	30–45 min	1–3 h	Useful to prevent and treat sedative/opioid withdrawal
					Effective antihypertensive
Dexmedetomidine[b]	0.3–1 mcg/kg	0.2–1 mcg/kg/h	10–20 min	30–60 min	Minimal respiratory depression
					Bradycardia with rapid bolus
					Useful for non-painful procedural sedation
Chloral hydrate	30–100 mg/kg	N/A	20–30 min	6–8 h	Long-acting mild sedative
					Toxic effects due to accumulation of active metabolite
					Do not use with liver/kidney dysfunction

[a]See text for more detailed information on additional routes. Dosing based on IV bolus and infusions where appropriate
[b]Based on slow bolus over 10 min

at therapeutic doses. Acute hemodynamic decompensation can occur even at therapeutic doses in children with preexisting cardiac dysfunction or hypovolemia or in those classified as poor metabolizers. Common adverse reactions include nausea, constipation, and dry mouth. Histamine-mediated adverse effects such as pruritus, urticaria, and bronchospasm are most often associated with morphine administration but may occur with other opiates as well.

Up until the second month of life, the hepatic CYP system is immature and may lead to prolonged clearance and elimination of opioids metabolized by this pathway.

27.5.2 Morphine

Morphine is the prototypic opiate. It acts on the μ receptors and can be given via enteral, rectal, SQ, IM, intrathecal, and epidural routes. It has a high enteral bioavailability but undergoes extensive first-pass effect in the liver. The IV to enteral dosing ratio is approximately 1:3. Morphine is less protein bound in infants (18–22%) than in adults (30%) and as such may lead to apnea if high initial doses are used. Morphine is primarily metabolized by hepatic phase II glucuronidation into an inactive metabolite, morphine-3-glucuronide, and an active metabolite, morphine-6-glucuronide. Both undergo renal elimination. Accumulation of morphine-6-glucuronide in children with renal insufficiency may cause adverse effects including respiratory depression. With IV administration, histamine-related vasodilatation may result in localized injection site erythema or generalized flushing and pruritus. Morphine-induced histamine release may result in exacerbations of allergic asthma and wheezing in susceptible children.

Morphine-6-glucuronide is an active metabolite of morphine that can be toxic and lead to respiratory depression, particularly in patients with kidney dysfunction.

27.5.3 Fentanyl

Fentanyl, a synthetic derivative of meperidine, is a commonly used opioid in the PICU. It is usually given via IV route but can be given SQ or IM. Fentanyl is 50–100 times more potent than morphine and has less hypnotic and sedative effects. It is extremely lipophilic and is a potent μ receptor agonist. Fentanyl, like other highly lipophilic drugs, has a rapid onset (30 s) and short duration (30–45 min) due to rapid penetration into the CNS and redistribution into fat. Thus, with initial dosing of fentanyl, the onset and duration are distribution dependent. After recurrent intermittent doses or continuous infusions, receptor saturation in lipophilic tissues leads to a prolonged elimination half-life and as such the duration of fentanyl effects become elimination dependent. Fentanyl is metabolized by the CYP3A4 isoenzyme into inactive metabolites that are renally cleared. Inhibitors (e.g., fluconazole) and inducers (e.g., phenytoin) of CYP3A4 may affect the magnitude and duration of clinical drug effect.

Fentanyl is well tolerated in children with renal dysfunction and requires dose adjustment only in advanced disease. Fentanyl is well tolerated in mild hepatic dysfunction as well. Fentanyl pharmacokinetics are most affected in disease states where hepatic blood flow is reduced such as that which may occur during low cardiac output.

Rapid boluses with fentanyl can cause chest wall rigidity and an inability to effectively oxygenate or ventilate. The onset of chest wall rigidity requires rapid airway and breathing intervention and the administration of naloxone or alternatively neuromuscular blockade.

Respiratory depression is dose dependent and minimal at typical doses needed for adequate analgesia. Fentanyl has a favorable hemodynamic profile and is generally well tolerated. Children with depressed cardiac function or hypovolemia are at increased risk for further hemodynamic compromise with high doses of fentanyl; therefore, low initial doses are recommended. Bradycardia may occur after rapid bolus. Fentanyl is highly bound to α1-acid glycoproteins in plasma, which are reduced in newborns. The fraction of unbound drug is increased in infants as compared to older children; therefore, lower initial doses should be used. Fentanyl is rarely associated with histamine release and is well suited to the child with a suspected allergy to morphine.

Fentanyl dosing for painful procedures or as an adjunct to sedative medications is typically 0.5–1 mcg/kg. Infusion rates of 0.5–2 mcg/kg/h are well tolerated. Boluses should be infused slowly over 1–5 min to decrease the possibility of chest wall rigidity (more often seen with doses greater than 5 mcg/kg).

27.5.4 Remifentanil

Remifentanil is metabolized by serum and tissue esterases, has an ultra-short half-life, and does not require bolus dosing.

Remifentanil is a very short-acting opioid that acts at the μ receptor. It is administered only via the intravenous route. Metabolism occurs via tissue and plasma esterases into an inactive metabolite, remifentanil acid, that is renally cleared. Remifentanil has a rapid onset of action similar to fentanyl and is 250–500 times as potent as morphine. Because it is metabolized mainly in the plasma, rather than redistributed, the half-life ($T_{1/2}$) is only 5–10 min. A steady state can be achieved after only 10–15 min of continuous infusion. Bolusing is not necessary, and an increase in analgesia and sedation can be achieved solely with a change in infusion rate. The short half-life of remifentanil allows rapid recovery, making it an attractive choice for neurologically impaired patients in whom awakening for serial evaluations is desired. Remifentanil is a potent respiratory depressant. It should be used cautiously in the unintubated child. Remifentanil has a stable cardiac profile similar to fentanyl but can also be associated with bradycardia during rapid infusion. Dosing adjustments are not necessary in patients with renal or liver dysfunction, even when severe.

27.5.5 Hydromorphone

Hydromorphone (Dilaudid), a derivative of morphine, has similar selectivity for μ receptors. It can be given by enteral, SQ, or epidural routes but most commonly is administered via the IV route. It is five to seven times more potent than morphine and more lipophilic, leading to a longer duration of action (4–6 h). Metabolism occurs via glucuronidation to hydromorphone-3-glucuronide. Accumulation of this metabolite in patients with renal compromise may cause neuroexcitation leading to myoclonus or seizures. The metabolite does not have opioid activity and therefore does not cause increased morphine-like effects in the presence of renal dysfunction. Reduced dosing should be considered in children with advanced renal or hepatic dysfunction.

Hydromorphone causes less pruritus, dysphoria, nausea, and sedation than morphine while providing excellent analgesia. Hydromorphone is frequently used for postoperative patient-controlled analgesia and to treat refractory pain associated with cancer. Dose-dependent respiratory depression can occur, especially if dosing is frequent, owing to its long duration of action. Hydromorphone should be used cautiously in children with myocardial dysfunction.

27.5.6 Methadone

Methadone has a long half-life, and dosing frequency should be sequentially decreased once steady state is achieved.

Methadone is an opioid that traditionally has been used to treat or wean opioid-dependent patients. Its main activity occurs via the μ receptor, but it also binds weakly to the glutamatergic NMDA (N-methyl-d-aspartate) receptor and thus acts as a glutamate receptor antagonist. Methadone undergoes phase I N-demethylation via CYP pathways 3A4 and 2D6. Like other drugs metabolized by multiple CYP enzymes, methadone is prone to drug-drug interactions. Methadone may cause prolongation of the QT interval. Serial electrocardiograms should be monitored with prolonged or high-dose therapy. Metabolites are inactive and renally excreted. Methadone has the longest duration of action of any opioid. It has a high bioavailability (80–90%) after enteral administration. It can be given via IV and IM routes but is commonly used enterally for long-term analgesia (such as in palliative care) and to facilitate weaning of opioid-dependent patients.

27.5.7 Non-opioid Analgesics

Mild to moderate pain may be controlled without the use of opioids. There are many antipyretic analgesics commonly used in the PICU. Acetaminophen (paracetamol) has analgesic and antipyretic activities but relatively few anti-inflammatory effects. Like the nonsteroidal anti-inflammatory (NSAID) medications, acetaminophen exhibits its effect through blocking prostaglandin production via inhibition of cyclooxygenase enzymes (types 1, 2, and 3). It is administered via enteral (15 mg/kg), rectal (15–20 mg/kg), or IV (15 mg/kg) routes. Current data does not suggest superior analgesia or antipyretic control from IV dosing compared to enteral or rectal dosing. In the child that is unable to tolerate enteral meds, it may be a reasonable choice for non-narcotic analgesia. Maximal recommended daily dose, regardless of route, is 3000 mg. Caution must be used to ensure overdosing does not occur. Acetaminophen-induced liver failure is the most common cause of acute liver failure in children greater than 3 years of age. It is not the parent compound but rather its metabolite (*N*-acetyl-*p*-benzo-quinone imine, NAPQI) that causes hepatocellular damage via exhaustion of glutathione reserves.

Trilisate is a potent NSAID that is not associated with platelet dysfunction and may be useful in the pediatric oncology population.

The NSAID medications used in children include ibuprofen, naproxen, diclofenac, salicylate (aspirin), and trisalicylate (Trilisate). Enteral and rectal routes are most common, while ketorolac (Toradol) is the only approved IV administered NSAID in the United States. NSAIDS are excellent in the treatment of pain due to inflammation. Ketorolac is a very effective anti-inflammatory agent, and its use in the postoperative patient often has an opioid-sparing effect. The epidemic of opioid addiction has led to an increased use of both enteral and IV NSAIDs in postoperative pain management. High-dose NSAIDs should be avoided in patients with preexisting kidney disease as they may inhibit prostaglandin regulation of renal blood flow. In general, NSAIDs should be used with caution in children with liver dysfunction, renal dysfunction, coagulopathy disorders, thrombocytopenia, or active bleeding. Aspirin, one of the oldest known analgesics, is rarely used to treat pain in pediatric hospitals due to its association with Reye syndrome. It can also cause serious GI irritation and can decrease platelet function. Trilisate, also known as choline magnesium trisalicylate, is an aspirin-like drug that provides the same anti-inflammatory, antipyretic, and analgesic effects, but does not impair platelet function. While not routinely prescribed, it may be used safely in oncology patients where other NSAIDS would not be tolerated.

Table 27.6 Opioid analgesics

Drug	Bolus[a]	Infusion[a]	Onset	Duration	Comments
Morphine	0.05–0.1 mg/kg	0.025–0.1 mg/kg/h	2–5 min	2–4 h	Least lipid soluble
					Histamine-related vasodilation may cause hypotension
					Infants at high risk for respiratory depression
Fentanyl	0.5–1 mcg/kg	1–5 mcg/kg/h	0.5–1 min	15–30 min	Well tolerated in mild hepatic and renal dysfunction
					Minimal histamine release
					Muscle rigidity with rapid, high-dose bolus
Remifentanil	0.5–1 mcg/kg	0.05–0.25 mcg/kg/min	0.5–1 min	5–10 min	Metabolized by plasma and tissue esterases
					Rapid onset and clearance
Hydromorphone	0.02 mg/kg	0.01–0.015 mg/kg/h	10–15 min	4–6 h	Less sedative effects than most opioids
					No histamine release or pruritus
Methadone	0.1 mg/kg	N/A	10–15 min	12–36 h	Long duration even after single dose
					No active metabolites
					Used to treat and prevent drug withdrawal

[a]See text for more detailed information on additional routes. Dosing based on IV bolus and infusions

27.5.8 Opioid Antagonist

The most commonly used opiate antagonist is naloxone. Naloxone works by directly blocking the opioid binding site on the μ receptor. It can reverse the sedative and analgesic effects of opioids in a dose-dependent fashion. Opioid-induced respiratory depression is treated with 1–5 mcg/kg of naloxone and repeated as necessary. Owing to naloxone's short half-life, cumulative dose of 10 mcg/kg may be required. Opioid overdose requires dosing in the range of 10–100 mcg/kg with a max single dose of 2 mg. Continuous infusion may also be indicated in patients that require frequent prn dosing. Naloxone may also be used to counteract the systemic side effects of epidural opioids such as pruritus (Table 27.6).

27.6 Tolerance and Dependence

Tolerance is the need to increase the dose of an opioid or BNZ to achieve the same analgesic or sedative effect that had previously occurred at a lower dose. Mechanisms involved in its development include receptor desensitization and upregulation of excitatory intracellular pathways. It most commonly occurs in patients receiving fentanyl but can be seen with all opioids and BNZs. The phenomenon of cross tolerance allows the provider to rotate between opioids and still achieve a desired analgesic effect without escalating the total dose.

Careful calculation of equipotent dosing should occur when rotating opioids to prevent sub- or supra-therapeutic dosing.

Physical dependence may develop with repeated or prolonged administration of opiates and or BNZs. Physical dependence is a physiologic state in which the drug cessation leads to withdrawal symptoms. It typically occurs after greater than 1 week of therapy but may develop in a shorter period of time. Symptoms become apparent within 24 h and peak at approximately 72 h after cessation.

27.7 Benzodiazepine and Opioid Withdrawal: Prevention and Treatment

Withdrawal symptoms can be classified into three categories: CNS stimulation, sympathetic nervous system activation, and GI disturbances.

The prevalence of withdrawal in PICUs varies widely, with reports ranging from 45% to 86%. Withdrawal symptoms can be classified into three categories. CNS stimulation may cause agitation, confusion, hallucinations, tremors, movement disorders, seizures, and sleep disturbances. Sympathetic nervous system activation may lead to hypertension, tachycardia, tachypnea, diaphoresis, and dilated pupils. GI disturbances include poor feeding, enteral feeding intolerance, diarrhea, abdominal cramping/pain, nausea, and vomiting. Fever is also a symptom that can occur during withdrawal. It is often difficult to discriminate the signs and symptoms of withdrawal from the child's ongoing disease process. Therefore, the diagnosis of withdrawal should be made after excluding other organic causes of the new symptoms.

Multiple scoring tools have been used to identify the child experiencing withdrawal. The earliest scoring tools were originally developed for neonates experiencing withdrawal as a result of maternal opioid addiction. Both the Finnegan Score and the simpler Lipsitz score have been validated in infants but may not be applicable in older children. Assessment tools for withdrawal in critically ill children do exist but currently lack the universal acceptance afforded the neonatal abstinence scales. The opioid and benzodiazepine withdrawal scale (OBWS) was developed as a modified version of a neonatal abstinence tool. The 21-item checklist revealed good inter-rater and content validity and was later revised to the 12-item Withdrawal Assessment Tool 1 (WAT-1). The WAT-1 has been found to have high sensitivity and specificity for identifying opioid withdrawal; however, it does not discriminate between opioid and benzodiazepine withdrawal symptoms. The Sophia Observational withdrawal Symptom scale (SOS) identified the co-occurrences of withdrawal symptoms in critically ill children on continuous benzodiazepine and/or opioid infusions for greater than 5 days.

A recent multi-institutional study (RESTORE) found that using a nurse-implemented, goal-directed sedation protocol, compared to usual PICU care, led to fewer days of opioid administration and exposure to fewer sedative classes and patients were awake and calm more days while ventilated. The intervention did not lead to a decrease in total ventilation days, as was the author's primary objective. Children at risk for withdrawal typically receive prolonged intermittent doses or continuous infusion of sedatives and/or opioids. The duration of drug exposure and the development of withdrawal symptoms vary from child to child, though it has long been accepted that the cumulative dose (dose × duration) is a strong determinant. There currently lacks a clear cutoff for duration of therapy and risk of withdrawal. Data to suggest useful cutoffs are derived from observation and retrospective studies and vary greatly from institution to institution. Nonetheless, review of the available literature would suggest opioid therapy >5 days or BNZ therapy between 5 and 10 days is predictive for developing withdrawal.

A widely accepted practice is to begin enteral therapy at the onset of IV weaning.

Multiple weaning strategies exist to allow safe discontinuation of opioids and BNZs. While there is no consensus on methods of weaning, data does show that having a formal weaning protocol in place not only decreases the amount and duration of drug exposure, but it can also lead to a decrease in drug-related adverse events. This has been shown to occur across the spectrum of patient demographics including CICU, surgical subspecialty patients, and children with critical illness. To initiate any weaning protocol, a conversion of total daily parenteral dose to an equipotent enteral dose is required. It is accepted practice to begin either enteral therapy at the onset of parenteral weaning or replace the short-acting IV drug (fentanyl or midazolam) with a longer-acting IV drug (methadone or lorazepam, respectively). Methadone is most commonly used to wean from short-acting IV opioid infusions, but morphine and hydromorphone have been used successfully as well. Enteral and IV lorazepam are typically used to wean from short-acting BNZ infusions, with agents like diazepam or clonazepam much less commonly used. Weaning durations can vary greatly (2–40 days). Current data support a duration of at least 5 days with the most typical duration lasting 10 days. Longer duration of IV opioid or BNZ therapy will require a longer weaning period. Slow reduction in the enteral or long-acting IV dosing can occur by 10–20% each day but may need to be adjusted based on individual response. It is not uncommon to need prn IV dosing during the weaning process. Regardless of the chosen agents or planned duration used for weaning, frequent reassessments are required to identify signs and symptoms of breakthrough withdrawal.

Alpha 2 adrenergic agonists clonidine and dexmedetomidine can be used to facilitate weaning from opioids and BNZ.

Other medications used to prevent and treat opioid/benzodiazepine withdrawal include the α_2 adrenergic receptor agonists clonidine and dexmedetomidine. The α_2 adrenergic and μ opioid receptors activate the same K^+ channel via inhibitory G proteins. This common site of action may account for the efficacy of α_2 agonists in treating opioid withdrawal. Data to support this class of drug for either opioid or BNZ withdrawal is limited to case reports and small observational studies. In the child who has been on a prolonged dexmedetomidine infusion, clonidine may be used to treat withdrawal symptoms that occur during the weaning process.

Withdrawal from sedative and analgesic medications is common in the PICU and can be associated with significant morbidity. Proactive approaches can help prevent and rapidly identify children at risk for undergoing withdrawal. Recent recommendations from an expert panel to prevent and treat opioid withdrawal are summarized in ▶ Box 27.2.

Box 27.2 Key Elements in the Prevention of Opioid Tolerance and Treatment of Opioid Withdrawal

- Opioid doses should match the intensity and frequency of pain. Doses should be carefully titrated to the minimum effective dose
- Short-acting opioids should be used for procedural or breakthrough pain, whereas longer-acting opioids should be used for prolonged or chronic pain
- Avoid opioid use if only sedation is required
- The assessment of opioid withdrawal should occur in PICU patients who have had prolonged use of opioids. Current assessment tools include the Withdrawal Assessment Tool-1 (WAT-1) and Sophia Observational withdrawal Symptom scale (SOS)
- Management of opioid withdrawal includes gradual opioid tapering, environmental and nursing supportive measures, and treatment with methadone and clonidine or dexmedetomidine
- Prevention of opioid tolerance includes nurse-controlled sedation, rotation of drug type, use of neuraxial (i.e., epidural) opioids, and, when safe, daily interruption of continuous infusions

27.8 Conclusions

Relieving anxiety and pain in critically ill children is one of the most important and rewarding interventions that can occur in the PICU. The provision of sedation and analgesia for children undergoing painful and non-painful procedures outside the PICU is occurring more frequently and often involves the pediatric intensivist. A thorough understanding of the commonly used sedatives and analgesics is essential and includes knowledge of clinical pharmacology, drug-drug interactions, and potential adverse reactions. Pediatric intensivists must also be cognizant of drug dependence and potential withdrawal with prolonged use of opioids and BNZs.

Review Questions

1. *An 8-year-old 30 kg boy is transported to the PICU from a community hospital with the presumptive diagnosis of sepsis. He is noted to have scattered purpuric lesions over his legs and abdomen. His vital signs are as follows: T 39.5 C, HR 160, RR 40, BP 76/32, SpO_2 90% on 100% oxygen via NRB mask. He requires fluid resuscitation, inotropic support, and mechanical ventilation. His hemodynamics have improved and current vitals are 38.5 C, HR 128, RR 24, BP 96/52, SpO2 99%. He is given 3 mg IV versed and 60 mcg IV fentanyl to facilitate arterial line placement. He again becomes hypotensive to 71/34 and requires an additional 20 mL/kg NS to restore perfusion and blood pressure. Which statement is most correct?*
   A. Use of ketamine due to its direct positive inotropic effect would have avoided the hemodynamic instability seen after versed/fentanyl administration.
   B. Use of ketamine for sedation and analgesia is contraindicated in sepsis due to causing adrenal suppression.
   C. Use of versed and/or fentanyl is contraindicated in patients with hemodynamic instability.
   D. Versed and fentanyl in the doses given were unlikely to affect the child's hemodynamics, and the likely cause for the hypotension was progressive cardiovascular dysfunction.
   E. When using benzodiazepines and opioids in the setting of hemodynamic instability, low initial doses should be used and subsequently titrated as tolerated.

2. *Which of the following medications can be used to treat mild to moderate pain and is not associated with platelet dysfunction?*
   A. Ibuprofen
   B. Naproxen sodium
   C. Toradol
   D. Trisalicylate
   E. Salicylic acid

3. *Which statement regarding the Mallampati classification is most correct?*
   A. Assignment of a Mallampati class is best done by asking the child to open his mouth fully, protrude his tongue, and vocalize "ahh" to better visualize the tonsils.
   B. Mallampati classification has been used to help predict difficult intubation in adults based on visualization of pharyngeal structures.
   C. Mallampati classification has been validated as an accurate predictor of adverse airway events during procedural sedation in children.

D. Mallampati classification predicts patients at risk for laryngospasm.
E. Mallampati classification should be done while the patient is supine.

4. *A 2-year-old girl with a history of biliary atresia and failed Kasai procedure is admitted to the PICU with respiratory distress secondary to respiratory syncytial virus pneumonia. She has severe liver dysfunction and is awaiting liver transplantation. She is mechanically ventilated and agitated. Which statement regarding the choice of an appropriate benzodiazepine is most correct?*
   A. Lorazepam hepatic metabolism occurs mainly by phase II reactions and is less affected by liver impairment than midazolam.
   B. Lorazepam hepatic metabolism occurs mainly by phase I reactions and therefore is prone to multiple drug-drug interactions.
   C. Midazolam and lorazepam both undergo hepatic phase I and phase II metabolism and are contraindicated in patients with moderate liver dysfunction.
   D. Midazolam metabolism occurs mainly by phase II reactions and therefore is prone to multiple drug-drug interactions.
   E. Midazolam metabolism occurs mainly by phase 1 reactions that produce several inactive metabolites that are renally excreted.

5. *Propofol is administered to facilitate a brain MRI in a 6-year-old boy with a new-onset seizure disorder. Which of the following correctly describes a potential adverse effect of propofol?*
   A. Blood pressure is generally maintained, but bradycardia is common due to direct vagal stimulation.
   B. Endotracheal intubation is required during deep sedation with propofol due to commonly seen loss of airway reflexes and apnea.
   C. Pain at the site of injection is common due to propofol's low pH.
   D. Peripheral compartment saturation is unlikely to occur during procedural sedation.
   E. Propofol is contraindicated in children with seizure disorders due to its pro-epileptic effects.

6. *A 6-month-old 5 kg girl with congenital CMV and chronic liver disease is brought to the PICU for management of second- and third-degree burns over her abdomen and chest sustained after an accidental hot water spill. She is in significant pain but remains alert and stable on 2 L oxygen via NC. She is given two 1 mg doses of morphine 10 min apart and shortly thereafter becomes somnolent and hypopneic and SpO2 drops to 70%. She requires brief bag mask ventilation but quickly recovers. Which of the following statement is most correct regarding her respiratory decompensation?*
   A. Due to the infant's immature CYP 450 metabolism, morphine quickly accumulated after her repeated dosing.
   B. Infants are more prone to the respiratory depressant effects of morphine due to the presence of a higher density of μ2 receptors when compared to older children.
   C. Infants are more prone to the respiratory depressant effects of morphine due to a higher free fraction of available drug as protein binding is less in infants than in older children.
   D. Morphine-6-glucuronide, an active metabolite of the parent drug, is likely responsible for her respiratory depression.
   E. Morphine-3-glucuronide, an active metabolite of the parent drug, is likely responsible for her respiratory depression.

7. *Which of the following is an accurate statement regarding remifentanil?*
   A. Active metabolites may accumulate with renal insufficiency.
   B. Histamine release and vasodilation may cause hypotension.
   C. Metabolism occurs via hepatic phase II conjugation.
   D. Metabolism occurs via hepatic phase I reactions.
   E. Metabolism occurs via plasma esterases.

8. *Which statement best describes the property of the antagonist drug?*
   A. Flumazenil, a serotonin receptor antagonist, can be used to reverse the clinical effects of benzodiazepines.
   B. Flumazenil's long half-life allows reversal of clinical toxicity while awaiting complete metabolism of the benzodiazepine.
   C. Naloxone works by selectively blocking the μ2 receptor.
   D. Naloxone's long half-life allows reversal of clinical toxicity while awaiting complete metabolism of the opioid.
   E. Low-dose naloxone may be used to counteract pruritus seen with morphine.

Answers

1. E
2. D
3. B
4. A
5. D
6. C
7. E
8. E

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Neuromuscular Blockade

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Contents

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Learning Objectives

At the conclusion of reading this chapter, the reader should have an understanding of:

- The indications for neuromuscular blockade in the pediatric intensive care unit (PICU) and the necessary co-administered therapies
- The pediatric pharmacology of neuromuscular blockade
- The physiology of the neuromuscular junction and how it is affected by neuromuscular blockade
- The specific neuromuscular blocking agents and reversal agents used in the PICU including their pharmacokinetics, pharmacodynamics, and adverse effects
- The interactions and adverse effects of neuromuscular blockade including ICU myopathy
- The need and mechanisms for the monitoring of neuromuscular blockade
- The agents used for the reversal of neuromuscular blockade

28.1 Introduction

Neuromuscular blocking agents (NMB) are frequently used in the pediatric intensive care unit (PICU), and their use has been correlated with severity of illness measures. While their use may be associated with improvements in measured physiologic variables, these agents are also associated with multiple and potentially fatal adverse effects. A thorough understanding of the physiology and pharmacology of neuromuscular blockade is required for the safe and effective use of these medications.

This chapter will discuss the indications for the use of NMB and the associated issues involved in the administration of NMB to critically ill infants and children. The physiology of the neuromuscular junction will be reviewed, and the mechanisms through which that physiology is changed by NMB to produce their desired effects will be highlighted. Specific depolarizing and non-depolarizing agents will be described. The potential for myopathy associated with prolonged use of NMB will be illustrated, as will the use of nerve stimulation to monitor the depth of neuromuscular blockade. Finally, the medications used to reverse the effects of NMB will also be described.

28.2 Indications and General Issues

The decision to pharmacologically paralyze a child is not one that should be taken lightly. Few drugs are associated with such a risk of morbidity and mortality when inappropriately applied. Conversely, with sufficient preparation, experience, judgment, and expertise, the judicious use of NMB may produce significant improvements in the care and condition of critically ill infants and children. For this reason, the clinician must carefully weigh the risk and potential benefit before implementing a NMB.

Many indications are recognized for NMB use in the PICU (▶ Box 28.1), although published evidence for efficacy is incomplete. Some of the more common processes that can be facilitated with NMB include endotracheal intubation, mechanical ventilation, and invasive procedures. NMB may also be prescribed in an attempt to decrease the metabolic demand for oxygen.

Box 28.1 Indications for Neuromuscular Blockade in the PICU

- Facilitation of mechanical ventilation
- Decreasing oxygen consumption
- Endotracheal intubation
- Facilitation of invasive procedures
- Prevent manifestations of agitation
- Prevent shivering
- Treatment of intracranial hypertension
- Treatment of tetanus
- Protection of delicate surgical repairs
- Preventing removal of critical therapeutic devices (endotracheal tube, ECMO cannula, etc.)

One of the most common indications for the use of NMB in the PICU is to facilitate endotracheal intubation. When deciding to induce paralysis in this situation, the clinician must remember that there will be situations in which it will be safer for the patient to retain the ability to ventilate spontaneously. For a patient with evidence of upper airway obstruction, the use of NMB must be approached with caution. In the presence of craniofacial anomalies, the use of NMB is relatively contraindicated due to the increased likelihood of failed intubation and a lost airway. In addition, the use of NMB is contraindicated in any patient with an anterior mediastinal mass. In general, NMB should not be used to facilitate intubation unless the physician is confident in his ability to noninvasively ventilate the patient with bag-valve-mask ventilation.

When used appropriately, neuromuscular blockade optimizes conditions for intubation, facilitates mechanical ventilation and invasive procedures, and prevents self-harm.

Administration of muscle relaxants in the absence of adequate preparation to secure the airway and provide positive pressure ventilation can be disastrous. Personnel experienced in the intubation of infants and children, functioning equipment for intubation including backup equipment for potentially difficult intubations, and equipment for ventilation including a ventilator and a bag-valve-mask must be present and tested before administering NMB. With adequate preparation, the use of NMB makes intubation of the trachea easier and less traumatic. Administration of NMB improves laryngoscopic view, decreases time to securing the airway, and decreases the probability of unintended extubation.

Neuromuscular blockers may be helpful in facilitating ventilation in patients with severe lung dysfunction.

Another common indication for NMB is to facilitate mechanical ventilation. Sedation alone is occasionally inadequate to optimize conditions for ventilation, particularly in patients who are difficult to oxygenate and ventilate, as well as those who require non-physiological modes of ventilation. Patients who require hypo- or hypercarbia as part of their therapy may be more effectively ventilated with the use of NMB. The use of NMB may eliminate dyssynchrony with the ventilator, thereby improving pulmonary mechanics and minimizing ventilator pressures and the associated barotrauma. By preventing marked increases in trans-pulmonary pressures, use of NMB may decrease barotrauma and the risk of pneumothorax. In addition, patients receiving non-conventional modes of ventilation such as high-frequency oscillation may benefit from the use of NMB. Moreover, the elimination of ventilatory asynchrony may decrease the risk of intraventricular hemorrhage in preterm neonates, most likely by eliminating changes in intrathoracic pressure with resultant alterations in cerebral arterial and venous pressures. NMB are also administered to children being mechanically ventilated in order to increase oxygen delivery, decrease oxygen consumption, and decrease intracranial pressure.

Published evidence supporting much of this use is limited. A recent Cochrane review found evidence to support paralysis only in the case of neonates who exhibit asynchronous respiratory effort. A more recent study showed improved oxygenation index in patients in acute hypoxemic respiratory failure with NMB use. However, other studies found no consistent benefit of NMB in oxygen delivery, oxygen consumption, or chest wall compliance in ventilated patients.

Muscle relaxants can significantly improve conditions for invasive procedures in the PICU and improve safety.

Many infants and children in the intensive care setting require invasive procedures, such as central venous catheter placement, thoracentesis and/or chest tube placement, or bronchoscopy. For most procedures, patient immobility not only facilitates the performance of the procedure but also significantly decreases the probability of complications. Short-term paralysis in the intubated and ventilated patient for this purpose is often indicated, provided that adequate analgesia and sedation are also administered. In addition, muscle relaxation may attenuate the increase in oxygen consumption and hemodynamic changes that often accompany these procedures.

Often patients in the PICU have the potential to do themselves serious harm with movement, purposeful or otherwise. Sedation alone may be inadequate to prevent patients from removing venous and arterial catheters, endotracheal tubes, or even ECMO cannulae with resultant catastrophic hemorrhage, loss of respiratory and hemodynamic support, and possible mortality. Patients who have undergone certain surgical procedures such as tracheal reconstruction or cardiac surgery with an open chest will be at greater risk of injury from excessive movement and will benefit from the inability to move with NMB use.

28.3 Pharmacology of Muscle Relaxants in Children

General pharmacological principles are reviewed in ▶ Chap. 6, but some points regarding the pharmacokinetics and pharmacodynamics of NMB in infants and children should be emphasized.

Children, especially neonates, have a larger volume of distribution for neuromuscular blocking agents than adults.

The increased volume of distribution of neuromuscular blockers in infants is offset by the increased sensitivity of their neuromuscular junction.

The muscles of neonates are more sensitive to neuromuscular blockers than older children and adults.

Neonates, and to a lesser extent, infants and children have a significantly higher proportion of extracellular water than adults. For children, the volume of distribution for the very water-soluble drugs that produce neuromuscular blockade is larger than that of adults. This difference is most marked in neonates, particularly in premature infants. Conversely, neonatal muscles are more sensitive to the effects of NMB than those of adults and older children, most likely due to the immaturity of the neuromuscular junction. The balance of these effects generally results in an increased response to similar doses of relaxants in neonates (especially premature infants) and a decreased sensitivity in older infants and children. This balance also depends in part on the particular drug being used as will be discussed in the section regarding specific agents. The elimination mechanisms for these drugs, whether renal, hepatic, or by plasma esterase, may be immature in neonates, with a resultant longer duration of action, particularly in critically ill patients whose organ function is compromised by their illness.

28.3.1 Dosage and Administration

The doses of NMB are typically expressed as the "intubating dose" and "maintenance doses." The manufacturer's recommended "intubating dose" of a muscle relaxant is usually the dose calculated to rapidly and reliably produce complete flaccidity for the purpose of endotracheal intubation. The ED_{95} is the Effective Dose that produces complete flaccidity in 95% of a population. The recommended intubating dose is often twice the ED_{95}, but may be more or less, depending on the side effect profile of the drug. For example, the recommended intubating dose of d-tubocurarine, 0.5–0.6 mg/kg, is the same as, or only slightly more than, the ED_{95} (0.5 mg/kg) because this dose produces significant histamine release. In contrast, the recommended intubating dose of cisatracurium, 0.15–0.2 mg/kg, is 3–4 times the ED_{95}, since a dose twice the ED_{95} will have a relatively slow onset. It should be understood that in a patient who is already intubated and ventilated, it is unnecessary to administer an "intubating dose" of most NMB even if the goal is to produce complete flaccidity. It is reasonable to start with a dose somewhat less than the ED_{95} and to assess the block prior to further dosing (see section on monitoring of neuromuscular blockade). Recommended "maintenance doses" for NMB are typically one third to one half of the ED_{95} and should be carefully titrated based on monitoring. Continuous infusions are another acceptable means of maintaining neuromuscular blockade, but careful monitoring is again a requirement.

NMB doses are typically described as an intubating dose and maintenance dose. Intubating doses are usually multiples of the ED_{95}, and maintenance doses are 1/3 to 1/2 the intubating dose.

Although it may seem unnecessary to mention that NMB produce no sedation or analgesia, the point cannot be overemphasized. It is absolutely necessary that patients receiving NMB in the PICU also receive adequate sedation and analgesia appropriate for their physiologic status. NMB must not be a substitute for sedative/analgesic medication. Once patients have been pharmacologically paralyzed, caregivers must maintain an even higher level of vigilance as the patient will be unable to communicate anxiety, fear, or pain. Occasionally, patients are unable to tolerate much sedation due to hemodynamic instability, but this should not be an excuse for failing to provide any sedation or analgesia.

Patients paralyzed with NMB in the ICU must also receive sedation, as NMB have no CNS-depressant properties and awareness and recall are devastating complications.

28.4 Physiology of the Neuromuscular Junction

The neuromuscular junction (NMJ) is examined in detail in ▶ Chap. 23 but will be reviewed briefly here. The axon of a motor neuron arborizes into multiple branches as it approaches the muscle it innervates. Each branch terminates at a neuromuscular junction composed of the axonal presynaptic terminal, the motor end plate on the muscle cell, and the synaptic cleft or gap between the two cells. The presynaptic terminal is a metabolically active area responsible for the manufacture, reuptake, packaging, and release of acetylcholine. When an action potential reaches the presynaptic terminal, channel-mediated calcium entry facilitates the release of hundreds of thousands to millions of acetylcholine molecules into the synaptic cleft. The motor end plate is typically located centrally in a muscle fiber and contains millions of nicotinic acetylcholine receptors (ACRs). These receptors are transmembrane proteins composed of five subunits. Binding of two acetylcholine molecules to the receptor causes conformational changes in the receptor that promotes the flow of sodium and calcium into and potassium out of the cell. When a sufficient fraction of ACRs become activated, the depolarization wave passes to ion channels throughout the muscle cell, resulting in calcium influx and release of stored calcium from the sarcoplasmic reticulum. The rise in intracellular cal-

When the action potential of a motor neuron arrives at the presynaptic terminal, it causes the release of acetylcholine into the synaptic cleft.

Sodium channels surrounding the motor end plate are responsible for conducting the end plate depolarization to the rest of the myocyte. This initiates myofibril depolarization, calcium entry, and contraction.

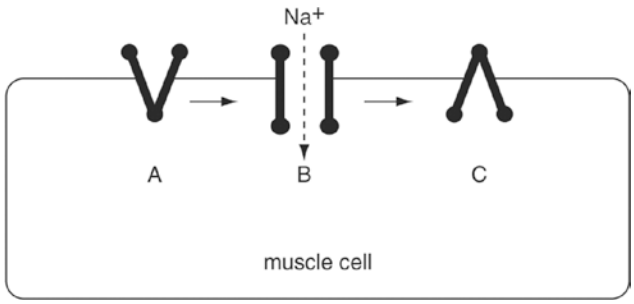

Fig. 28.1 Diagram of peri-endplate sodium channels cycling from closed/ready (**a**) to open (**b**) to fixed closed (**c**) conformations. Repolarization of the end plate allows reconfirmation from "c" to "a"

cium reduces the inhibition of troponin and facilitates actin-myosin interactions which result in the contraction of the muscle fiber.

Non-depolarizing neuromuscular blockers act by competing with the binding of acetylcholine to receptors on the motor end plate.

Acetylcholine rapidly diffuses away from the motor end plate and is hydrolyzed by the enzyme acetylcholinesterase which is present in high concentration in the synaptic cleft. When acetylcholine is no longer bound to an ACR, the receptor returns to a resting state and the motor end plate repolarizes. Sodium channels that surround the motor end plate promulgate the action potential cycle rapidly from closed/ready to open to a fixed closed conformation (◘ Fig. 28.1). End plate repolarization allows return of these channels to a closed/ready state, but prolonged depolarization on the end plate maintains the channels in a fixed closed conformation, effectively preventing further propagated action potentials and contraction.

Nicotinic ACRs are also present on the presynaptic membrane, where they function in a positive feedback mechanism to increase the availability of acetylcholine in response to an action potential. This allows the release of adequate amounts of acetylcholine during high-need situations.

All NMB share structural characteristics with acetylcholine which allow them to bind to the ACR. Depolarizing NMB cause activation of the motor end plate when bound to the ACR. Non-depolarizing NMB also bind to ACR, but do not induce the conformation changes necessary for ion flux. Instead, they bind competitively with acetylcholine, preventing activation. The relative concentrations of the drug and the transmitter determine the net effect at the motor end plate. Non-depolarizing NMB also have effects on presynaptic ACRs, inhibiting the positive feedback increase in acetylcholine availability. There is a wide margin of safety in neuromuscular transmission such that over 50% of ACRs must be blocked before an effect is measurable with electrical stimulation. Termination of the effect of depolarizing and non-depolarizing NMB depends on the diffusion of the drug away from the synaptic cleft and back into the plasma space where it is subject to elimination via various pathways described in the following section.

28.5 Specific Agents

28.5.1 Depolarizing Agents

Succinylcholine (SUX) is the only currently available depolarizing NMB. Few drugs have generated as much controversy as SUX because of the significant side effects associated with its use.

28.5.2 Mechanism of Action and Kinetics

The onset of paralysis after intravenous succinylcholine is approximately 30 s in infants and children.

The succinylcholine molecule is essentially two acetylcholine molecules connected at their acetate methyl ends. SUX binds to the ACR and induces the same conformational changes and depolarization of the motor end plate that

acetylcholine does. SUX, however, is not hydrolyzed by acetylcholinesterase when it diffuses into the synaptic cleft. Therefore, it is able to bind repetitively to the ACR, causing prolonged activation of the motor end plate and fixation of peri-junctional sodium channels in the fixed closed state.

Succinylcholine binds to the acetylcholine receptors on the motor end plate, producing prolonged depolarization.

Onset of neuromuscular blockade following an intravenous dose is more rapid with SUX than any other NMB. Following a 2 mg/kg dose, 95% paralysis will be achieved in 28 s in infants and 36 s in children. Relaxation is typically preceded by an increase in muscle tone, associated with fasciculations, as individual muscle fibers depolarize. The ED_{95} for neonates is 0.62 mg/kg; for infants, 0.73 mg/kg; and for children, 0.42 mg/kg. SUX may also be administered intramuscularly. An intramuscular dose of 4 mg/kg produces flaccid paralysis in 3–4 min and recovery in about 20 min, although some characteristics of prolonged block may be observed (see phase 2 block, below).

Succinylcholine activity is terminated by metabolism by plasma cholinesterase (pseudocholinesterase).

Termination of depolarization produced by SUX depends on the diffusion of the drug away from the NMJ and back into the plasma, where it is rapidly hydrolyzed to succinate and choline by plasma cholinesterase, also known as butyrylcholinesterase or pseudocholinesterase. Plasma cholinesterase has such a high capacity for SUX degradation that it has been estimated that only 10% of an intravenously administered dose reaches the NMJ. Following an intravenous dose of 2 mg/kg, 90% recovery will occur in 6.5 min in infants and 6.2 min in children.

28.5.3 Cholinesterase Deficiency and Dysfunction

The recovery times listed above for SUX are relevant only to the majority of patients who have a normal quantity and quality of circulating plasma cholinesterase. Children have essentially the same level of cholinesterase activity as adults, but have a significantly decreased duration of succinylcholine effect, due to their higher relative cardiac output in redistributing SUX for metabolism. Patients may have genetic or acquired defects in cholinesterase production that produce a prolonged effect from SUX.

Many drugs and conditions interfere with plasma cholinesterase function, but have only modest effects on the duration of action of succinylcholine.

Plasma cholinesterase is synthesized in the liver, and production may be limited by a number of conditions and medications. Hepatic insufficiency, pregnancy, malnutrition, large-area burns, cancer, and use of oral contraceptives, metoclopramide, esmolol, and some cytotoxic drugs produce significant decreases in cholinesterase activity, but only modest and clinically unimportant increases in the duration of SUX action. Abnormally low cholinesterase activity may be present in some preterm neonates, but activity does not correlate with gestational age and typically normalizes within 2 weeks of birth.

Organophosphate poisoning, particularly when acute and severe, may markedly increase the duration of apnea following SUX administration. Certain drugs used to antagonize the effects of non-depolarizing NMB inhibit plasma cholinesterase in addition to their inhibition of acetylcholinesterase and may modestly prolong the effects of SUX. Neostigmine and pyridostigmine roughly double the duration of SUX-induced paralysis, while edrophonium has little effect. Echothiophate, which is used topically for esotropia in children, irreversibly inhibits cholinesterase by an average of 48% but up to 86% after 8 weeks on the drug.

Genetic variants of plasma cholinesterase, often referred to as "cholinesterase deficiency," may have a marked effect on prolonging paralysis from succinylcholine.

Although SUX metabolism occurs within an acceptable time period despite wide variation in plasma levels of cholinesterase, patients who have a genetically altered enzyme may have markedly prolonged effects. The production of plasma cholinesterase is controlled by a single gene on chromosome 3, and single amino acid substitutions produce an enzyme with significantly altered ability to degrade SUX. Several abnormal genetic variants have been identified

with the most common being A, atypical (dibucaine-resistant); F, fluoride-resistant; and S, silent. Dibucaine-resistant atypical cholinesterase is the most common genetic variant with an incidence as high as 1 in 25 for heterozygous individuals in northern European populations. It is less common in other European and American Caucasian populations (1 in 60) and even less common in African-American (1 in 200) and Asian (1 in 350) populations. The heterozygous F and S genotypes occur in approximately 1 in 200 individuals. Heterozygotes have only moderately prolonged paralysis after SUX, while homozygous A, F, or S individuals have marked prolongation of effect. Mixtures of abnormal enzyme types (e.g., A/S) also metabolize SUX very slowly.

In vitro testing for plasma cholinesterase activity is difficult, as atypical cholinesterases that have virtually no activity with SUX retain some ability to hydrolyze commonly used substitute enzyme substrates such as benzoylcholine. As a result of this, atypical cholinesterases are commonly described by the ability of other chemicals to inhibit their activity. Dibucaine is a local anesthetic that is no longer in clinical use. Normal cholinesterase activity is inhibited by 80% in the presence of dibucaine and is reported to have a *dibucaine number* of 80. The dibucaine number of homozygous atypical enzyme (A/A) is only 20, while heterozygotes have an intermediate number. Fluoride may be used in a similar manner to identify a fluoride-resistant abnormal enzyme. Homozygous F/F enzyme has a fluoride number of 15–25, while that of normal enzyme is 60.

28.5.4 Adverse Effects of Succinylcholine

Hyperkalemia is a rare but potentially fatal complication of succinylcholine, more common in immobilized ICU patients, in burn or crush injury,and in certain neuromuscular diseases.

Hyperkalemia Because of its depolarizing mechanism of action, SUX increases potassium flux from intracellular to extracellular fluid and typically produces an increase in plasma potassium of about 0.5 mEq/L in adults, with lesser changes in children. Patients with denervating diseases or injury, burns, or crush injury and those who have severe systemic infection or have been immobilized in the PICU may have an exaggerated hyperkalemic response to SUX which may be life-threatening. Patients with neuromuscular diseases such as Duchenne muscular dystrophy are also likely to have severe hyperkalemia in response to SUX, and as such, the drug is contraindicated in these patients. A burn injury of a single limb which correlates roughly to 8–9% body surface area is enough to cause an increase of potassium >9 mEq/L and is associated with cardiac arrest. It is the general consensus that succinylcholine should not be administered beyond 24 h after a burn injury.

From 1990 through 1992, the FDA received a series of 14 case reports of hyperkalemic cardiac arrests in children after they received SUX. The FDA assembled a review team and, after evaluation of the evidence, changed the SUX package insert to specifically contraindicate the elective use of SUX in pediatric patients, except in those cases where it was clearly needed. However, after much protest and further consideration, the package insert was revised again and now contains a "black box" warning stating: "WARNING: RISK OF CARDIAC ARREST FROM HYPERKALEMIC RHABDOMYOLYSIS," with the recommendation "…that the use of succinylcholine in children should be reserved for emergency intubation or instances where immediate securing of the airway is necessary…."

Succinylcholine-induced hyperkalemia is due to ion flux through abnormal extrajunctional acetylcholine receptors.

The pathophysiology shared by patients at high risk for SUX-induced hyperkalemia is an increase in extrajunctional ACRs. Under normal conditions, the vast majority of ACRs are located in the NMJ. Under certain conditions such as those listed above, ACRs increase in density and are expressed along the length

of the muscle fiber. Activation of these extrajunctional receptors is most likely responsible for the exaggerated hyperkalemic response to SUX.

Malignant hyperthermia (MH) is a serious disorder of myocyte calcium modulation that results in excessive contraction, heat production, uncoupling of oxidative phosphorylation, and eventually rhabdomyolysis and life-threatening hyperkalemia. Mortality rates remain high at approximately 10% since 1985, even with widely available information about MH and a specific drug treatment in dantrolene. Dantrolene acts by directly decreasing calcium release from the sarcoplasmic reticulum, thereby decreasing excitation-contraction coupling. There is a multifactorial genetic predisposition for MH, and it is commonly triggered by inhaled anesthetics as well as by SUX. It is more common in children than in adults and is more common in males than in females. Patients with certain musculoskeletal syndromes such as central core, King-Denborough, multiminicore, and centronuclear myopathy disease are at high risk for MH, and the appropriate precautions should be taken with these patients.

Malignant hyperthermia is a rare, potentially fatal syndrome that may be triggered by succinylcholine. Patients with certain musculoskeletal syndromes are at high risk for MH.

Signs and symptoms of MH are listed in ◘ Table 28.1. A high index of suspicion must be maintained for MH when SUX is administered to any child. Appropriate treatment includes the immediate administration of dantrolene, 2.5 mg/kg, intravenously (IV), followed by titrating additional doses as indicated by response. Supportive care, aimed at avoidance of cardiorespiratory collapse and renal failure, must be aggressive. An excellent resource for MH is the Malignant Hyperthermia Association of the United States (MHAUS) at ► www.mhaus.org.

The Malignant Hyperthermia Association of the United States (MHAUS - 7 www.mhaus.org) is an excellent resource for MH.

Contracture testing (caffeine-halothane contracture test) is considered the gold standard test to determine MH susceptibility. It requires a skeletal muscle biopsy from the patient's thigh to assess muscle contractile properties upon exposure to ryanodine receptor agonists such as caffeine and halothane. The sensitivity of the test is 100%; however, the specificity is 80% with 20% false positives. Furthermore, the testing is expensive, and it requires the patient to travel to one of only four testing centers in the country. Genetic testing can also determine if the patient has the presence of a causative mutation diagnostic for MH susceptibility. Currently caffeine-halothane contracture test (CHCT) is recommended for the patient with:

- Known MH-susceptible relative as determined by a positive CHCT test
- A MH-susceptible relative (without positive RYR1 causative genetic mutation)
- A past suspected MH event
- Severe masseter muscle rigidity with a triggering agent
- Mild to moderate masseter muscle rigidity and rhabdomyolysis

◘ Table 28.1 Signs and symptoms of malignant hyperthermia

Tachycardia	Hyperthermia
Muscle rigidity	Hypertension
Respiratory acidosis	Hypercarbia
Metabolic acidosis	Hyperkalemia
Tachypnea	Hypercalcemia
Arrhythmias	Increased serum lactate
Myoglobinuria	Markedly increased creatine kinase

Rigidity of the muscles of mastication after succinylcholine administration is most commonly benign, but may presage malignant hyperthermia.

Masseter muscle rigidity is the increase in tension in muscles of mastication that sometimes occurs in patients, particularly children, after the administration of SUX. There has been much controversy over the implications of masseter muscle rigidity, with many suggesting that masseter muscle rigidity is indicative of a predisposition to MH and others arguing that masseter muscle rigidity is a normal phenomenon of SUX administration. Muscle biopsy contracture testing in patients with a history of masseter muscle rigidity has revealed a 50–60% incidence of MH susceptibility. It has been demonstrated that increased tension of the muscles of mastication is essentially universal in children given SUX. In 1 report, none of the 24 patients who received SUX developed MH including 3 who required multiple attempts at intubation due to difficult mouth opening. On the other hand, multiple reports describe patients with masseter muscle rigidity who subsequently developed MH. Although the implication of masseter muscle rigidity is unclear, it appears prudent to closely monitor patients who develop masseter muscle rigidity for the development of MH.

Succinylcholine administration in infants and small children should be preceded by an intravenous anticholinergic drug such as atropine or glycopyrrolate to prevent bradycardia.

Autonomic Effects Common to all NMB, SUX is effective because it is able to mimic acetylcholine. With SUX, this effect extends beyond the NMJ to include autonomic ganglia and parasympathetic muscarinic receptors. This results in a variable degree of activation of both sympathetic and parasympathetic nervous systems. The balance of these contradictory forces is largely influenced by the pre-existing physiology of the patient. In adults, intravenous SUX typically induces mild hypertension and tachycardia. Children and especially infants are parasympathetic dominant, and as such, SUX tends to induce bradycardia. Because the bradycardia is mediated primarily by stimulation of cardiac muscarinic receptors, prior administration of an anticholinergic agent can prevent the bradycardia. Atropine 10–20 mcg/kg is typically effective. Repeat doses of SUX are even more likely to precipitate bradycardia, or even asystole, in adults as well as in children. SUX administered intramuscularly is much less likely to cause bradycardia.

Succinylcholine may transiently increase intracranial, intragastric, and intraocular pressure, but the clinical significance of these increases is minimal.

Intracranial, Intraocular, and Intragastric Pressures SUX has the potential to transiently increase the pressure within various body compartments. It has been shown to increase cerebral blood flow, most likely through a combination of increased cerebral metabolic activity, increased carbon dioxide, and sympathetic stimulation. Although this could precipitate a rise in intracranial pressure (ICP), studies have found no such increase in patients at risk for increased ICP. SUX has also been found to increase intraocular pressure after intravenous or intramuscular administration in infants and children as well as in adults. The increase in pressure peaks at 2–4 min after intravenous injection and lasts approximately 6 min. Although this effect was originally thought to be due to increased tension of the extraocular muscles, it has been observed when the muscles have been detached from the globe and may result from changes in anterior chamber fluid flux. Although this may seem to contraindicate the use of SUX in patients with open globe injuries, extensive experience has shown that SUX can be safely administered in the setting of an open eye without loss of intraocular contents.

SUX also increases intragastric pressure, although inconsistently and not appreciably in infants and children. This effect appears related to abdominal wall fasciculation. The muscarinic effects of SUX increase gastroesophageal sphincter tone, which may counter the increase in intragastric pressure and reduce any increased risk of vomiting and aspiration.

Most of these increased body compartment pressure effects can be attenuated or eliminated by prior administration of a defasciculating dose (typically

10% of the ED_{95}) of a non-depolarizing NMB. The beneficial effects of SUX must be weighed against the increased body compartment pressures when deciding to use the drug. Avoidance of NMB with resultant failure to rapidly secure the airway, coughing during laryngoscopy, or bucking on the endotracheal tube will have more significant adverse effects on intracranial and intraocular pressures and increase the risk of aspiration to a greater extent than the use of SUX.

Histamine Release Like many NMB, SUX may directly release histamine from mast cells, potentially eliciting bronchospasm, arterial vasodilation, and increased capillary permeability.

Myalgias and Fasciculation Adolescent and adult patients with normal muscle mass will typically have diffuse muscle fasciculation after receiving an intravenous dose of SUX. This is the result of all individual muscle fibers contracting before relaxation due to prolonged depolarization. These fasciculations may or may not be related to the common occurrence of myalgias seen in patients treated with SUX. Myalgias are more common in younger patients having ambulatory surgery, possibly because these patients are more mobile and less likely to be receiving potent analgesic medications. Although the overall reported incidence is extremely variable, myalgias probably occur in at least 50% of patients given SUX. The incidence of myalgias may be decreased by prior treatment with a defasciculating dose of a non-depolarizing NMB administered 2–3 min before the SUX. Lidocaine may be equally or more efficacious.

Succinylcholine-induced myalgias are a common adverse effect of the drug that primarily affects patients receiving the drug for outpatient procedures.

SUX often causes an increase in serum creatine kinase and myoglobin levels, particularly when halothane is co-administered. The relationship of this phenomenon to MH is unclear.

Phase 2 Block Patients given large intramuscular doses, or, more commonly, those maintained on SUX infusions, occasionally develop a more protracted neuromuscular block with features of non-depolarizing block, such as a fade on train-of-four testing. This phenomenon is called a "phase 2 block" and is explained by the following mechanism: The administration of succinylcholine causes a continuous activation of the acetylcholine receptors at the neuromuscular junction resulting in a constant influx of sodium into the cell and potassium out of the cell. With doses of succinylcholine >4 mg/kg, this activity is prolonged. However, in spite of the continuous depolarization of the nerve cell, the postjunctional membrane potential moves towards the resting state due to an increased activity of the sodium potassium ATPase pump. Even with the occupation of the acetylcholine receptor by succinylcholine, the ATPase pumps sodium outside of the cell and potassium into the cell which moves the membrane potential in the direction of normal. As a result, the acetylcholine receptor does not respond appropriately to acetylcholine. The result is a neuromuscular blockade with the characteristics of a non-depolarizing neuromuscular blocker. This block can be antagonized by acetylcholinesterase inhibitors if necessary but will resolve over time.

28.6 Recommendations for Use

Succinylcholine is the most rapidly acting neuromuscular blocker and is indicated when rapid paralysis is necessary, usually for securing the airway.

Despite the many adverse effects of SUX, some of which may be life-threatening, the drug remains in clinical use for a single reason: there is no non-depolarizing NMB that produces conditions for endotracheal intubation as rapidly and then wears off so quickly. These two factors make SUX the drug

of choice (barring absolute contraindications) for situations requiring rapid paralysis to achieve acceptable intubating conditions, with the potential for rapid recovery should attempts at intubation fail. Prior to the elective use of SUX in a child, one should carefully weigh the potential risks and benefits of the drug. Specifically, the absolute need for rapid paralysis and reversal must be weighed against the small but very real risk of a fatal reaction. If only rapid onset is desired and prolonged paralysis is not problematic, strong consideration should be given to substitution of a rapid-onset non-depolarizing drug. Rocuronium (0.9–1.2 mg/kg) produces excellent intubating conditions in most patients within 60 s with a very low incidence of adverse effects. With the availability of the reversal agent sugammadex (see below), it is possible to reverse the effects of large doses of rocuronium rapidly in the event of a failure to intubate.

Patients who suffer cardiac arrest immediately following succinylcholine administration should be treated aggressively for hyperkalemia until the potassium level is proven to be normal.

If the use of SUX is deemed necessary, an effective dose is 2–3 mg/kg in infants and 2 mg/kg in older children. Infants and young children should receive atropine 10–20 mcg/kg prior to SUX. Monitoring of the electrocardiogram is critical in diagnosing rhythm disturbances and hyperkalemia and should be in place prior to administration. Patients should be carefully observed for adverse effects for 12–24 h. If hemodynamic instability rapidly ensues, particularly in the setting of cardiac arrest, appropriate measures aimed at the treatment of hyperkalemia should be initiated without delay.

28.7 Non-depolarizing Neuromuscular Blockers

Non-depolarizing neuromuscular blockers are divided into two classes based on structure: benzylisoquinolines and aminosteroids.

Non-depolarizing (ND) NMB currently in clinical use are larger molecules typically with two quaternary amines (at physiologic pH) separated by complex organic constituents. In the benzylisoquinoline (BIQ) class of NMB, the amine moieties are separated by linear diester chains or benzyl esters. The aminosteroid (AS) drugs contain a steroid skeleton separating the amines. Important characteristics of clinically available ND NMB are listed in Table 28.2.

28.7.1 Benzylisoquinolines

d-Tubocurarine (curare) was isolated from the sap of an Amazonian vine after the effects of arrows tipped with that sap were observed. It was the first depolarizing muscle relaxant used clinically, but is no longer available.

Atracurium is a synthetic BIQ with a slow onset and intermediate duration of action. The drug was designed to degrade spontaneously in vivo at physiologic pH and temperature. This degradation, termed Hoffman elimination, is responsible for approximately one third of the elimination of atracurium. The remainder of the drug is metabolized by non-specific plasma esterases. This organ-independent elimination has made atracurium attractive for use in patients with multiorgan dysfunction. One of the products of Hoffman elimination, laudanosine, has been found to produce neuroexcitation in animals, and concern has been raised regarding the safety of atracurium particularly for use of atracurium as an infusion and in patients with renal failure since laudanosine requires renal elimination. Laudanosine levels in ICU patients treated with atracurium are significantly lower than those found to cause seizures in animals, and no significant excitatory effects have been found despite frequent

Table 28.2 Properties of non-depolarizing neuromuscular blocking agents

Drug	Atracurium	Cisatracurium	Pancuronium	Vecuronium	Rocuronium
ED_{95} infant (mcg/kg)	156	43	66–81	47	260(ED_{90})
ED_{95} child (mcg/kg)	354	47	93	70–81	290–340
Intubating dose infant (mg/kg)	0.3	0.2	0.1	0.1	0.3–0.6
Intubating dose child (mg/kg)	0.6	0.2	0.1	0.1–0.12	0.9–1.2
Onset (s)	124–162	120–180	126	68i 112c	30–60
Duration(min) (T95)	32–41	36–43.3	60–75	70i 22c	63.4–100.8
Drip (mcg/kg/h)	558	186–270	40–70	70	300–1000
Histamine release	++				
Heart rate increase			++		+
Elimination	Hoffman, NS esterases	Hoffman	80% R	70% H	H

dTC d-tubocurarine, *ED_{95}* Effective Dose that produces paralysis in 95% of patients. Duration is time from onset of paralysis to 95% recovery. *i* infant, *c* child, *R* renal, *H* hepatic, *NS* non-specific

study. Atracurium also releases histamine when given as a bolus to facilitate intubation. The degree of histamine release can be minimized by administering the drug over at least 30 s. Histamine release is not an issue with continuous infusions. The intermediate duration of action, low cost, and organ-independent elimination have made atracurium one of the most commonly used agents for neuromuscular blockade in the ICU.

Cisatracurium is a single isomer of atracurium that is significantly more potent than the parent compound. It has a similarly slow onset and an intermediate duration of action that is somewhat longer than atracurium. It also undergoes Hoffman degradation; however, it is not metabolized by plasma esterases. Cisatracurium does not cause histamine release, even when given in doses greatly exceeding the ED_{95}. Cisatracurium is also popular as a NMB for continuous infusion in the ICU, but offers no particular advantage above atracurium for this use.

28.7.2 Aminosteroids

Pancuronium has a long duration of action and commonly produces an increase in the heart rate through inhibition of cardiac vagal input.

Pancuronium is a long-acting NMB with slow onset of action. It has been used for years in pediatric patients. It is primarily eliminated by the kidneys and will have a prolonged effect in patients with renal dysfunction. Pancuronium produces a moderate 14–28% increase in heart rate and blood pressure in infants and children attributed to its ability to block cardiac muscarinic receptors. However, the observation that catecholamine levels also increase after pancuronium administration suggests that it may also increase sympathetic nervous system activity. Many clinicians find the hemodynamic side effects of pancuronium advantageous in off-setting the depressant effects of sedative and anesthetic medications, but drug-induced increases in blood pressure may theoretically be deleterious in premature neonates at risk for intracranial hemorrhage. Conversely, pancuronium has been found to decrease hemodynamic responses to nursery procedures.

Rocuronium has the most rapid onset of any non-depolarizing NMB and has only mild vagolytic effects.

Vecuronium is an aminosteroid NMB with an intermediate onset and duration of action in older children and adults of approximately 20 min. In infants, however, the duration of action is more than doubled with comparable dosing. Vecuronium is eliminated primarily through hepatic metabolism to several metabolites with variable potency as NMB. Some metabolites are sufficiently potent to cause prolonged weakness in ICU patients, particularly if renal dysfunction decreases their clearance. The drug is devoid of hemodynamic side effects and does not release histamine. It is packaged as a lyophilized powder that needs to be reconstituted with sterile water or saline prior to use.

Rocuronium is the most recently developed aminosteroid NMB. Like vecuronium, it has an intermediate duration of action in children and adults, but may be longer acting in neonates. Dosing tailored to the increased sensitivity to NMB of neonates may provide equivalent recovery. The primary benefit of rocuronium is its rapid onset. Intubating conditions equivalent to SUX (1.5 mg/kg) can be obtained 60 s after a rocuronium dose of 0.9 mg/kg in children and as little as 0.3 mg/kg in small infants. As with all NMB, larger doses generally accelerate onset, but necessarily prolong duration. Rocuronium has also been evaluated as an intramuscular agent. Although the drug was found to be effective via the intramuscular route, onset time was long (7.4 and 8 min in infants and children, respectively). Rocuronium is not an acceptable alternative to SUX for rapid attainment of acceptable intubating conditions in patients without intravenous access. Bolus dosing produces an increase in heart rate that is more modest than that due to pancuronium. Rocuronium is eliminated primarily through hepatic metabolism with some metabolites having NMB effects.

28.7.3 Interactions and Adverse Effects of Neuromuscular Blockade

A defasciculating dose of a non-depolarizing neuromuscular blocker is sometimes used to decrease the incidence of myalgias seen after administration of succinylcholine.

Caution should be observed when administering two different neuromuscular blockers together or in sequence as the effects may be exaggerated.

NMB are subject to numerous interactions with other drugs and pathologic states in critically ill pediatric patients. The administration of two different non-depolarizing NMB will have different effects depending on the order administered and the class of NMB (AS or BIQ). The co-administration of two drugs from the same class will have additive effects. The administration of a BIQ with an AS will have synergistic, i.e., greater than additive, effects. The combination of different drugs in sequence will produce an effect more like the first drug given. The duration of block produced will be closer to the expected duration of another dose of the first administered drug.

Patients treated for prolonged periods with neuromuscular blockers often develop tolerance to the drugs, requiring escalating doses to produce the same effect.

A small dose (10% of an intubating dose) of a non-depolarizing NMB is sometimes injected before SUX to decrease fasciculations and subsequent myalgias (see the section on succinylcholine). This "defasciculating" dose inhibits the development of the subsequent depolarizing block from succinylcholine such that the recommended intubating dose of succinylcholine is 50% higher after a defasciculating dose of a non-depolarizer. ◘ Table 28.3 lists the effect of several medications and clinical conditions on the duration and/or depth of NMB.

28.7.4 Tolerance

It has been frequently observed that tolerance develops after prolonged use of non-depolarizing muscle relaxants in the ICU, most likely due to proliferation of extrajunctional ACRs. This development of tolerance requires the use of increasing doses of neuromuscular blockade to maintain paralysis.

28.7.5 Myopathy

ICU patients treated with neuromuscular blockers are at risk for development of prolonged weakness due to myopathy.

NMB have been associated with the development of prolonged generalized weakness in the form of myopathy or nerve dysfunction (see also ▶ Chap. 24). Prospective and retrospective adult studies have found that as many as 70% of critically ill patients display generalized muscle weakness after treatment with NMB and 30% are significantly symptomatic. The precise incidence of generalized weakness in children is not known, but it is thought to be less common. One prospective PICU study reported an incidence of generalized weakness of 1.7% (14 of 830 patients) in children ages 3 months–17 years. Prolonged weakness or myopathy is a severe complication with significant morbidity. One case report describes an 8-year-old patient who required 13 months to return to normal strength. This patient initially had sensory deficits as well as significant motor weakness. This patient had an axonal motor neuropathy after treatment with vecuronium. Additionally, a diffuse necrotizing myopathy has also been described in association with NMB use. The aminosteroid muscle relaxants (pancuronium, vecuronium) have been more commonly associated with the development of a myopathy compared with the benzylisoquinolines.

Table 28.3 Effects of various drugs and conditions on neuromuscular blockade due to non-depolarizing muscle relaxants

Medications	Effect on block
Inhaled anesthetics	↑
Aminoglycosides, clindamycin, tetracyclines	↑
Local anesthetics	↑
Loop diuretics	↑
Quinidine, procainamide	↑
Phenytoin	↑
Dantrolene	↑
Azathioprine	↓
Steroids	↓
Lithium	↑
Magnesium	↑
Calcium	↓
Prolonged use of muscle relaxants	↓
Conditions	
Hypothermia	↑
Large burn injury	↓
Lower motor neuron injuries	↓
Cerebral palsy	↓
Muscular dystrophies	↑

The differential diagnosis of prolonged weakness in patients treated with neuromuscular blockers includes disuse atrophy, critical illness polyneuropathy, acute quadriplegic myopathy, and prolonged neuromuscular blockade.

Risk factors for the development of NMB-associated myopathy have been identified. The most commonly reported co-factor has been the concomitant administration of high-dose corticosteroids which by themselves may produce myopathy. The duration of NMB use does not appear to be an issue as myopathy has developed after as few as 4 or as many as 102 days of treatment. Both continuous infusion and bolus dosing have been implicated. Total doses, on a per kilogram basis, have typically been higher in patients developing myopathy compared with doses used during anesthesia. This observation may be accounted for by both the development of tolerance and by the fact that inhalational anesthetic agents, which increase NMB effects, are not administered in the PICU. Patients developing myopathy often have ARDS or sepsis as a diagnosis. In one series, greater than 50% of cases occurred in children undergoing solid organ or bone marrow transplantation.

The differential diagnosis for prolonged weakness after the use of NMB includes disuse atrophy, critical illness polyneuropathy, acute quadriplegic myopathy, or neuromuscular junction blockade. Electromyography (EMG), nerve conduction studies, muscle biopsy, and serum creatinine kinase (CK) measurement may be required to differentiate among these conditions.

Concomitant use of steroids appears to increase the risk of myopathy from neuromuscular blockers.

Disuse atrophy or acute myopathy is associated with generalized weakness of both proximal and distal muscles, although proximal muscles tend to be more affected. CK levels are markedly elevated, and muscle biopsy shows acute necrosis. Recovery is generally rapid (weeks). Critical illness polyneuropathy

presents as flaccid paralysis and typically involves the extremities (distal greater than proximal) more than the trunk. The cranial nerves are spared. In addition, distal sensory loss may also occur, and patients have markedly diminished or absent deep tendon reflexes. Nerve conduction studies may demonstrate both sensory and motor denervation. EMG studies are only mildly abnormal, and serum CK levels are normal. There are only a handful of definite case reports of critical illness polyneuropathy in children. From these case reports, it appears that the onset occurs earlier than that observed in adults (10 vs. 14 or more days, respectively). Fortunately, mortality in children appears to be less than in adults. Acute quadriplegic myopathy, sometimes referred to as critical illness myopathy, is associated with quadriparesis and affects the respiratory muscles in 25% of cases. Serum CK levels are mildly increased in 50% of cases. Nerve conduction studies reveal no sensory impairment and only mild motor delays. EMG demonstrates decreased motor action potential amplitude. Muscle biopsy results vary from isolated type II myofibril atrophy to necrosis of all fiber types. In adults, the development of acute quadriplegic myopathy is associated with a decrease in thick filament proteins within the muscle secondary to an absence in myosin messenger RNA as well as partial or complete loss of myosin or myosin-associated proteins. The variable loss of thick filament protein is not related to the dose or duration of NMB use in the ICU. Recovery from either critical illness polyneuropathy or acute quadriplegic myopathy is generally 3–6 months, but may be even longer.

Decreased physical activity and corticosteroid therapy prior to a critical illness are associated with a higher risk of myopathy. Steroid myopathy typically presents as mild proximal muscle weakness. In the setting of a critically ill patient receiving corticosteroids, it is hypothesized that a NMB or a metabolite may have direct myotoxic effects.

The incidence of myopathy or neuropathy in infants is probably very low given the paucity of case reports in neonates. The use of NMB in infants has been associated with decreased joint mobility and contractures, which suggests that the prophylactic use of physical therapy in patients receiving NMB is indicated. Prolonged weakness from the lingering effects of NMB at the NMJ may occur after short-term paralysis (1–3 days) with any of the aminosteroid NMB. Vecuronium and pancuronium have most commonly been reported to produce prolonged neuromuscular junction blockade. Prolonged blockade often occurs in patients with significant renal or hepatic dysfunction. Thus, either hepatic or renal dysfunction may prolong the effects of these drugs. Table 28.4 outlines the diagnostic findings of prolonged weakness in the critically ill patient.

Dysfunction of organs responsible for elimination of neuromuscular blockers may result in prolonged weakness not related to myopathy.

In light of the potential for the development of a NMB-related myopathy, it is prudent to use the minimum amount of muscle relaxant necessary. Frequent assessment of neuromuscular transmission is required for optimal safe use of continuous infusions of these drugs, but is often omitted due to unfamiliarity or lack of equipment. According to one survey, NMB were used in 31% of patients in the PICU; however, monitoring of blockade was performed in only 16% of those patients. Unfortunately, the survey did not differentiate between continuous infusion and intermittent dosing. Published case reports of NMB-associated myopathy in pediatric patients do not report the monitoring of blockade, and it can be presumed that it was not performed. A prospective study by the Mayo Clinic regarding their use of NMB indicated that NMB are used infrequently overall, but five times more often in pediatrics (5%) than in adults (1%). All patients treated with NMB at the Mayo Clinic are now routinely monitored for the extent of neuromuscular blockade.

Table 28.4 Diagnostic findings for prolonged weakness

Testing	Critical illness polyneuropathy	Critical illness myopathy	Neuromuscular junction blockade
Nerve conduction studies			
Motor amplitude	Reduced	Reduced	Normal
Motor CV	Nl to mildly decreased	Nl to mildly decreased	Normal
Sensory amplitude	Reduced	Normal	Normal
Sensory CV	Nl to mildly decreased	Normal	Normal
Needle electromyography			
Fibrillations	Distal mostly	Mild, moderate, diffuse	Normal
Motor action potential	Large, polyphasic	Small, brief	Normal
Repetitive muscle stimulation	Usually normal	Usually normal	Fade noted
Direct muscle stimulation	Response obtained	Minimal/no response	Response obtained

Nl normal, *CV* conduction velocity

28.8 Monitoring of Neuromuscular Blockade

Electrical nerve stimulation for monitoring of neuromuscular blockade may be accomplished with single twitch, train-of-four, tetanus, post-tetanic count, or double-burst stimulation.

The clinical effect of NMB should be monitored by stimulation of a peripheral motor nerve and measurement of the response of innervated muscles. The principle of monitoring is to evaluate the muscular response to a supramaximal stimulus delivered to a peripheral nerve. A supramaximal stimulus is a stimulus with enough intensity to ensure that all muscle fibers supplied by the nerve react. After administration of a NMB, the response of the muscle decreases in parallel with the number of receptors blocked. The reduction in response during constant stimulation reflects the degree of neuromuscular blockade. Electrical stimulation can easily be accomplished with a number of inexpensive, readily available devices (Fig. 28.2). Stimulation is commonly performed using one of four patterns: train of four (TOF), tetanic stimulation, post-tetanic count (PTC), and double burst (DB).

The TOF pattern is the most popular in studies as well as that used most frequently by anesthesiologists in practice. The TOF pattern involves delivering four supramaximal stimuli at 0.5 s intervals. With each stimulus in the train, the muscle contracts, but the intensity of the contraction decreases across the four stimuli in the presence of NMB (Fig. 28.3). The strength of the fourth contraction versus the first is the TOF ratio. The ratio is 1.0 at baseline without muscle relaxants. It is estimated that having one twitch out of four in response to TOF is associated with 90–95% occupancy of ACRs by the NMB. A TOF ratio of 0.1–0.2 is associated with 60–85% of receptors blocked. A TOF ratio of 0.9 must be reached to avoid clinically significant weakness. Unfortunately, visual or tactile evaluation of TOF ratios in excess of 0.7 is unreliable.

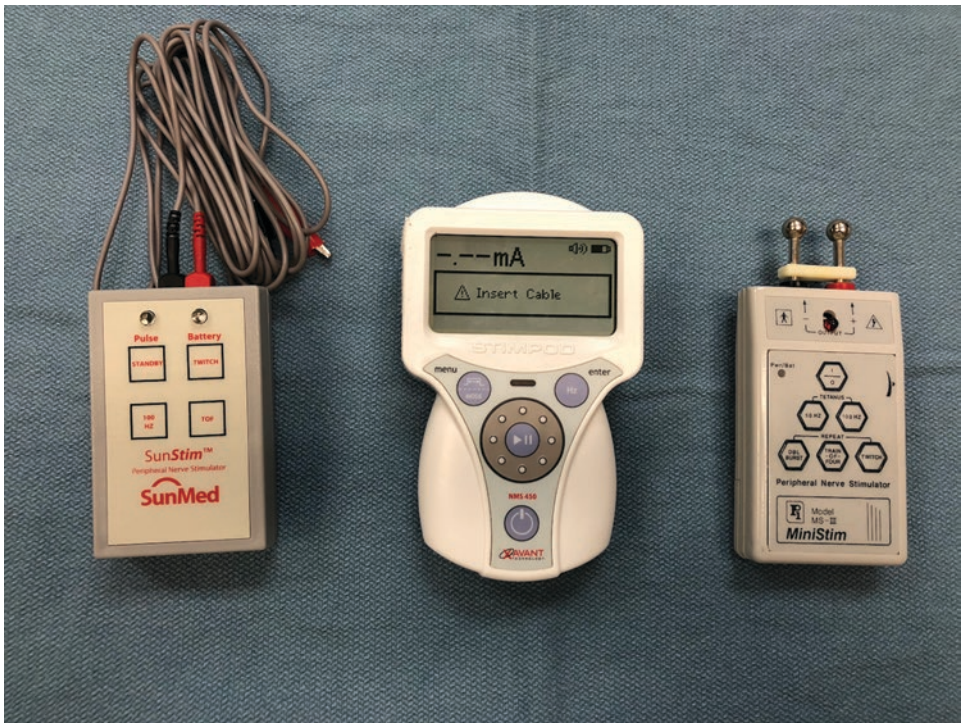

Fig. 28.2 Devices for monitoring of neuromuscular transmission. The devices on the left and right are inexpensive and readily available for application of train-of-four, single twitch, and tetanic stimulation. Stimulation can be delivered to the skin using removable metal ball electrodes (*right*) or wires with adhesive electrodes (*left*). The center device (Stimpod NMS450, Xavant Technology Ltd. Pretoria, South Africa) uses acceleromyography to quantitatively measure muscle responses to nerve stimulation

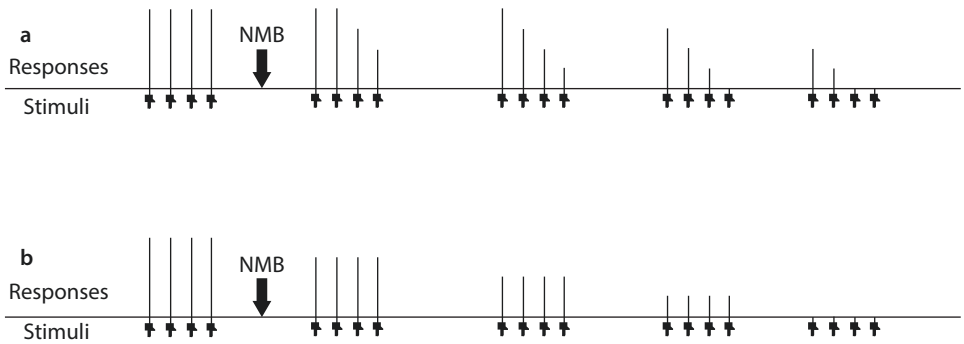

Fig. 28.3 Train-of-four (TOF) response to administration of a non-depolarizing **a** and depolarizing **b** neuromuscular blocker (NMB). *Arrows* below the horizontal line represent electrical stimulation of a peripheral nerve. Vertical lines above the horizontal line represent muscle responses to the stimuli. TOF ratio for the middle TOF in "**a**" would be 25%

Tetanic stimulation and post-tetanic count stimulation (PTC) are techniques useful to assess intense blockade before a response to TOF has reappeared. With both techniques, a more intense stimulus is applied. Tetanic stimulation at 50 or 100 Hz for 5 s is applied, and for PTC, this is followed by a stimulus of 1 Hz every second until muscle response is no longer observed. The number of contractions counted is the post-tetanic count. During recovery, the first post-tetanic response typically precedes the first TOF response by 5–10 min. A PTC of 6–7 indicates the imminent return of TOF responses. The tetanic stimulus results in large amounts of acetylcholine being mobilized presynaptically for subsequent release. Following an intubating dose of a NMB, there should be no response to tetanic stimulation, i.e., all receptors are blocked. With metabolism of the NMB and less postsynaptic blockade, a response to tetanic stimulation should appear in the form of a muscle contraction.

Tetanus and post-tetanic count are useful in assessing deeper levels of neuromuscular blockade.

Double-burst stimulation and quantitative measurement of train-of-four fade are the most sensitive tests for assessing the residual effects of neuromuscular blockers.

In contrast to tetanic stimulation, which is primarily used to assess intense blockade, double burst (DB) was found to be superior to TOF in assessing residual low-level muscular blockade. Tactile evaluation of "fade" is difficult to assess above a TOF ratio of 0.7. With DB, residual muscular blockade can be assessed via tactile evaluation up to a corresponding TOF ratio of 0.9. The increased sensitivity of DB was determined by comparing the subjective tactile technique used by most clinicians with objective recording methods.

Quantitative evaluation of NMB-induced blockade may be accomplished using mechanomyography (MMG), electromyography (EMG), or accelero-myography (AMG). Each of these methods has advantages and disadvantages. MMG has been the gold standard for neuromuscular monitoring in research. It is a time-consuming technique and requires significant calibration. EMG has the advantage of being easier to set up and can be used to evaluate muscles not accessible to mechanical recording. Good recordings can be obtained in most patients, although the results are not always reliable. There is a good correlation between MMG and EMG at baseline, but there are marked differences in the TOF ratio in response to non-depolarizing agents. Recently (March, 2018) a point-of-care EMG-based monitor has been approved by the FDA to quantitatively assess neuromuscular blockade (TwitchView™, Blink Device Company, Seattle, WA). AMG is based on Newton's second law: force equals mass times acceleration. If mass is constant, acceleration is directly proportional to force. The mass of the muscle being contracted should not change and the force generated would be dependent on the amount of blockade. Acceleration can then be analyzed and recorded using fairly simple equipment making it useful at the bedside (Fig. 28.2). There appears to be a reasonable correlation between TOF ratio measured by AMG and EMG or MMG; however, measurements with AMG are not directly comparable. Historically, most clinicians have monitored neuromuscular blockade using a subjective visual or tactile method. However with modern quantitative equipment, it is possible to more precisely measure low levels of neuromuscular blockade that are clinically significant. Understanding the factors that can influence the evoked response from a peripheral nerve stimulator will help the clinician achieve the desired level of paralysis.

Stimulation of the ulnar nerve while monitoring adductor pollicis is the best validated site for NMB monitoring.

The TOF ratio is useful in evaluating moderate blockade as is required for most surgical procedures and should be adequate for monitoring the ICU patient who requires continuous blockade. Typically, a TOF of 1–2 twitches out of 4 is maintained during surgery; however, the amount of blockade required for critical care is variable, being patient and disease dependent. Generally, the degree of blockade required in the ICU is believed to be less (i.e., 3–4 twitches out of 4 is probably adequate). Intense blockade is required to prevent coughing and bucking with tracheal intubation or tracheo-bronchial suctioning. The amount of blockade required to facilitate ventilation, such as that needed in the setting of ARDS or status asthmaticus, has not been determined. It should be noted that many PICUs have abandoned the use of continuous infusions of NMB for all but the most compromised patients, such as those on ECMO or HFOV, using intermittent dosing either as a supplement to sedation or as rescue during sedation breakthrough with sedation/paralysis algorithms guiding the interventions by experienced nursing staff. Indeed, one new approach to the continuous infusion of NMB in patients who cannot be permitted to breathe (HFOV) is to deliberately underdose the NMB continuous infusion such that the child emerges every few hours with minimal breathing efforts at which time small supplemental doses are given by protocol, thus avoiding progressive drug accumulation or continuous flaccidity with the attendant neuromuscular consequences.

For the purpose of monitoring continuous blockade, the ulnar nerve is the peripheral nerve most often stimulated in studies as well as that used primarily by clinicians. The median, posterior tibial, common peroneal, and facial nerves can also be used. The muscle groups stimulated by these nerves have different sensitivities to NMB. Results from one muscle group cannot necessarily be extrapolated to other muscles. As mentioned, the diaphragm is the most resistant of all muscles to depolarizing and non-depolarizing relaxants. The abdominal muscles, limb muscles, orbicularis oculi, masseter, geniohyoid muscle, and upper airway muscles are the most sensitive. The intercostals, larynx, and the corrugator supercilii are of intermediate resistance. Hence, blockade of the corrugator supercilii is a better reflection of diaphragmatic paralysis than the adductor pollicis.

Care must be taken during monitoring to avoid confusion of direct stimulation of a muscle with neuromuscular transmission.

When using a neuromuscular blockade monitor, care must be taken to discern muscle movement due to neuromuscular transmission from that due to direct electrical stimulation of a muscle. For example, when using the ulnar nerve, direct muscle stimulation can cause subtle movement of the fifth finger when no response in the thumb is present. When placing the electrodes of the nerve stimulator, the actual conducting area should be small, no more than 7–8 mm in diameter. If the area is too large, the current produced is dispersed and insufficient to stimulate the underlying nerve. ECG electrodes are readily available and acceptable for nerve stimulation. Figure 28.4 shows placement of the electrodes on the arm of an 8-year-old child. Neonatal ECG leads are frequently used on infants and small children. Figure 28.5 illustrates placement of electrodes on the arm of a 22-month-old boy. The negative electrode should be the more distal of the two. Even smaller electrodes or needle electrodes may be used in infants to prevent direct muscle stimulation. In infants, monitoring is especially difficult to interpret. Tetanic stimulation cannot be used in infants less than 12 weeks of age because fade and post-tetanic exhaustion occurs in neonates even in the absence of NMB. TOF monitoring can and should be performed in this patient population given their sensitivity to NMB.

In addition to understanding the varied muscle sensitivities to NMB, it is important to consider clinical conditions which can affect monitoring. Hypothermia can potentiate NMB and affect monitoring. Local surface cooling can result in different TOF ratios between a cold extremity and a contralateral warm extremity. Peripheral edema can increase skin impedance rendering

Hypothermia and edema may interfere with monitoring of neuromuscular blockade.

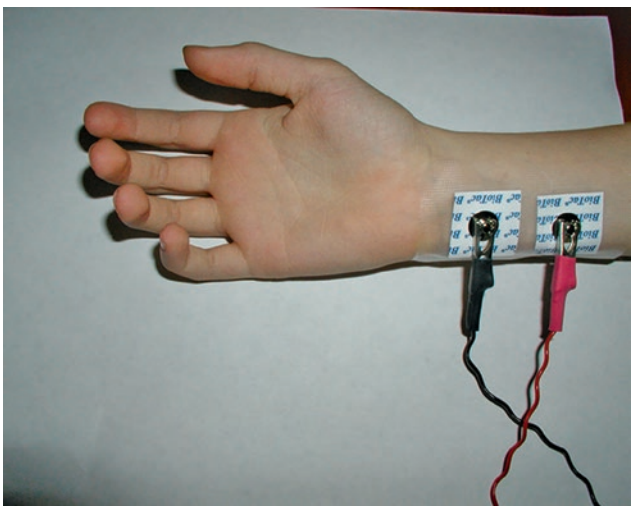

Fig. 28.4 Placement of electrodes for ulnar nerve stimulation. These are ECG leads and have a conducting surface of 10 mm which is greater than what is recommended

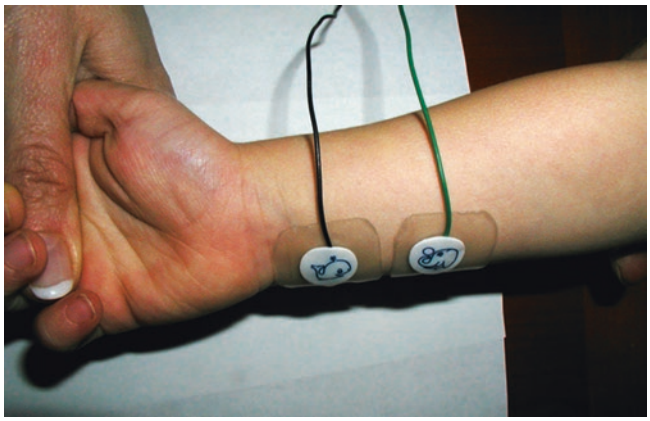

Fig. 28.5 Neonatal ECG electrodes on a 22-month-old boy for ulnar stimulation. Gentle retraction on the thumb is used for tactile evaluation of the evoked response

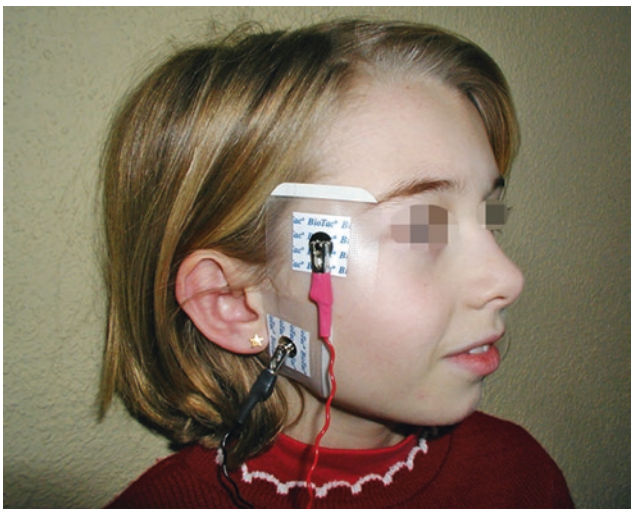

Fig. 28.6 Placement of electrodes for facial nerve monitoring (Note the black electrode which is the negative one is not the distal electrode as with the extremities)

monitoring equivocal. This problem was noted in a study correlating muscle movement with TOF scores in critically ill pediatric patients on NMB infusions. In the setting of significant edema, the facial nerve and orbicularis oculi or corrugator supercilii muscles may be used for monitoring. Alternatively, needle electrodes may be used with the ulnar nerve. With facial nerve monitoring, the negative electrode should be placed over the nerve and the positive electrode placed distally over the nerve between where it exits from the parotid gland and where it innervates the orbicularis oculi. Figure 28.6 illustrates correct placement of the electrodes for stimulation of the facial nerve on an 8-year-old girl.

Although evidence that monitoring of neuromuscular blockade improves outcomes is limited, monitoring is strongly recommended as the only objective means to determine dosing and avoid overdosage.

Although there is evidence that the presence of residual neuromuscular blockade after surgery is associated with an increased risk of postoperative respiratory complications and that this residual block can be measured, there is a paucity of data indicating that monitoring neuromuscular block improves outcomes. A prospective study of adults receiving continuous NMB infusion in the ICU demonstrated no difference in either the total dose of NMB or the

time to recovery between a group of patients who had TOF-based dosing and a group who received dosing based on a clinical assessment. The clinical assessment group, however, was monitored with a strict schedule for assessment of neuromuscular blockade with titration every 12 h. Although such careful attention to dosing based on clinical signs may lead to equivalent results with TOF monitoring, the literature is replete with case reports of prolonged paralysis in patients who had been treated according to subjective clinical observation. Therefore, monitoring is recommended for patients receiving continuous infusions of NMB as the most objective and simplest means of ensuring appropriate levels of neuromuscular blockade and minimizing prolonged paralysis. As a result of this, many ICUs are developing guidelines for the routine use of NMB in patients. In patients most at risk for complication, TOF monitoring of the patients on continuous NMB infusion should be performed routinely and considered another vital sign. Monitoring is especially important in the neonatal group where sedation and pain management strategies are less common and often less aggressive. In a 1993 review, 40% of NICU patients received no sedation while being paralyzed.

The use of NMB in critically ill ICU patients must be undertaken with great caution especially with regard to the use of continuous infusions of neuromuscular blocking agents. The benefit of prolonged continuous paralysis to facilitate mechanical ventilation or to maintain immobilization after surgical procedures may outweigh the risks of developing myopathy or neuropathy, but published evidence of such benefit is limited. Indeed, there is a large therapeutic ground between the infusion of NMB for continuous paralysis (in addition to appropriate sedation) and the use of no NMB at all with rapidly escalating sedative doses in attempt to control all fluctuations in state of arousal. At some PICUs, the majority of intubated patients receive combinations of continuous sedative infusions with intermittent doses of sedatives and NMB titrated by established algorithms. These PICUs utilize the philosophy that intermittent paralysis, if accompanied with sedation, is not inhumane and that judicious use of intermittent paralysis can often facilitate sedation and comfort when cycles of hypercarbia and agitation feed on themselves and need to be interrupted. Knowledge that patients in the PICU are at risk for myopathy or neuropathy and that the use of NMB increases that risk should signal the clinician to be ever vigilant for evidence of a problem when NMB are employed. Given that children may develop problems sooner than adults, evaluation for weakness separate from the effects of a NMB needs to begin earlier. Normal brainstem reflexes in the absence of deep tendon reflexes are particularly concerning and should prompt a thorough evaluation.

28.9 Reversal of Neuromuscular Blockade

The effects of non-depolarizing neuromuscular blockers may be reversed by the administration of drugs which inhibit acetylcholinesterase, overcoming the competitive blockade of receptors at the neuromuscular junction.

Drugs that "reverse" neuromuscular blockade are often administered after surgery to antagonize moderately deep levels of block in order to restore the patient's ability to maintain an airway and breathe normally. Reversal agents are of less utility in the ICU where it may be more acceptable to allow NMB to be metabolized or excreted over a few hours. Exceptions may occur in patients who are brought directly to the PICU from the operating room with residual neuromuscular blockade in whom rapid extubation is desirable (e.g., s/p Fontan procedure) or in a child needing temporary paralysis for a procedure or diagnostic study. Reversal agents in clinical use are acetylcholinesterase inhibitors or agents that bind the NMB and prevent it accessing the neuromuscular junction.

Neostigmine is the preferred drug to reverse longer-acting neuromuscular blockers. An anticholinergic drug must be administered with neostigmine or edrophonium to prevent severe adverse parasympathetic effects.

Acetylcholinesterase inhibitors have profound parasympathomimetic effects including bradycardia that require co-administration of an anticholinergic medication.

Edrophonium and neostigmine reversibly bind and inactivate acetylcholinesterase which leads to increased levels of acetylcholine at the neuromuscular junction. This increase in acetylcholine overcomes the competitive effects of the NMB. Edrophonium has a much faster onset than neostigmine, but a shorter duration of action, its half-life being only 10 min. Because of its short duration, it should not be used to antagonize long-acting NMB when a profound block is present, (i.e., one twitch out of four on TOF) because the effects of the NMB will return after the edrophonium has been metabolized. The dose required is greater in infants (0.6 mg/kg) and children (0.9–1 mg/kg) than in adults (0.5 mg/kg). Neostigmine has peak effect at about 7 min and has a much longer duration with a mean half-life of 53 min. Neostigmine can be given with more intense blockade than edrophonium without an increase in the time to a TOF ratio of 0.9. The dose of neostigmine is also greater in infants and children than in adults (25–75 mcg/kg vs. 10–60 mcg/kg respectively). As both drugs inhibit acetylcholinesterase at autonomic synapses as well as at the neuromuscular junction, reversal agents given alone will precipitate a profound increase in parasympathetic activity, manifested by gut hypermotility, salivation, and bradycardia. For this reason, an anticholinergic drug must be given with the reversal agent to attenuate cholinergic side effects. Glycopyrrolate (15 mcg/kg) is most often used with neostigmine, as the drugs have relatively similar pharmacokinetics. Many clinicians prefer to use atropine (20 mcg/kg) in pediatric patients, as they are reassured by the more significant effects of this drug on heart rate. Atropine is also better for use with edrophonium, as they both have rapid onset. The administration of 10 mcg/kg of atropine 30 s before edrophonium will minimize any change in heart rate.

Sugammadex has less hemodynamic effects than neostigmine and does not require the use of glycopyrrolate or atropine.

Sugammadex is a modified gamma cyclodextrin that forms a complex with the non-depolarizing neuromuscular blocking agents rocuronium and vecuronium. By forming this complex, sugammadex reduces the amount of neuromuscular blocking agent available to bind with the acetylcholine receptor at the neuromuscular junction. As a result, neuromuscular blockade is reversed. Recommended doses of sugammadex are 2 mg/kg given at the time of reappearance of 2 twitches on a train-of-four (TOF) stimulation or 4 mg/kg in the presence of 1–2 post-tetanic twitches. Recovery to a train-of-four ratio (T4/T1) of 0.9 is approximately 1.5 min after 2 mg/kg given for reversal at 2/4 twitches of TOF for rocuronium and approximately 3 min for a dose of 4 mg/kg given when 1–2 post-tetanic twitches can be measured. Recovery time for vecuronium is slightly longer, 3 min and 4.5 min, respectively, under the conditions listed above. When a 16 mg/kg of sugammadex is given for rapid reversal after a rapid sequence induction using rocuronium and no twitches are present, reversal takes 4.5 min. Sugammadex is not metabolized, and it is excreted in its unchanged form in the urine. Its elimination half-life is 2 h, and the estimated plasma clearance is 88 L/min. In the post-marketing experience, numerous incidents of bradycardia have been reported. In some cases these episodes lead to cardiac arrest shortly after the administration of sugammadex. These post-marketing adverse events related to bradycardia were not observed in the studies submitted for FDA approval. However, bradycardia has been added as a possible adverse effect of sugammadex on the package insert. Sugammadex may also cause an anaphylactic reaction with an incidence of 0.3%. Anaphylaxis generally occurs within minutes of administration, and risk increases with higher doses. There were also noted small statistically significant increases in prothrombin time and partial thromboplastin time; however, there appears to

be no clinically significant effect on bleeding in clinical studies and post-marketing experience. Sugammadex has been shown to bind progestogens in vitro and thus may interfere with the action of hormonal contraceptives. Patients on hormonal contraceptives receiving sugammadex should use alternative contraception for 7 days.

28.10 Conclusions

In summary, neuromuscular blocking agents are useful adjuncts in the care of pediatric patients in the intensive care unit, although there is a paucity of evidence to directly support measurable improvements in outcomes. There is ample evidence of significant and varied morbidity associated with their administration. Their safe use mandates a thorough understanding of the desired and adverse effects of these medications and constant careful monitoring of the patient. In general, NMB should be used for as short a period of time as possible and at as low a dose as is absolutely required to achieve the desired end.

Review Questions

1. *Which of the following is true regarding succinylcholine?*
   A. Succinylcholine is easily revered with neostigmine.
   B. Succinylcholine has no important hemodynamic effects in infants or children.
   C. Succinylcholine is rapidly metabolized to choline and succinate.
   D. Succinylcholine may be associated with dysrhythmias due to hypokalemia.
   E. Succinylcholine-induced block produces a train-of-four ratio <0.5.

2. *A 5-year-old female with acute respiratory distress syndrome is receiving intermittent vecuronium to facilitate mechanical ventilation. The administration of which of the following medications is likely to increase the depth of the neuromuscular block provided in this young girl?*
   A. Norepinephrine
   B. Fentanyl
   C. Magnesium
   D. Propofol
   E. Cefazolin

3. *A 15-year-old male with acute myelogenous leukemia status post allogeneic hematopoietic stem cell transplant is admitted to the pediatric intensive care unit for mechanical ventilation. The young man has multiple organ dysfunction syndrome and exhibits evidence of significant renal and hepatic dysfunction. His pulmonary compliance is such that he requires neuromuscular blockade to facilitate ventilation with acceptable inspiratory pressures. Which of the following medications is LEAST likely to have a prolonged effect because of his renal and hepatic dysfunction?*
   A. Cisatracurium
   B. Pancuronium
   C. Rocuronium
   D. Tubocurarine
   E. Vecuronium

4. *A 4 year old boy is admitted to the pediatric intensive care unit following formation of a total cavo-pulmonary connection (Fontan procedure). The cardiovascular surgeon wishes him extubated as soon as possible to minimize the effects of positive pressure on pulmonary blood flow. Consequently, you decide to reverse residual neuromuscular blockade to facilitate successful extubation. Which of the following are true regarding reversal of neuromuscular blockade?*
   A. Sugammadex is effective in reversing atracurium and cisatracurium.
   B. Edrophonium and atropine are an appropriate reversal combination for pancuronium.
   C. Neostigmine may be administered alone to reverse aminosteroids because of their vagolytic effects.
   D. Sugammadex is effective in reversing patients from deep block with rocuronium.
   E. Reversal of blockade is not necessary once the patient is fully awake.

5. *Which of the following muscles is most resistant to neuromuscular blockade?*
   A. Adductor pollicis
   B. Diaphragm
   C. Geniohyoid
   D. Masseter
   E. Orbicularis oculi

Answers

1. C

   Succinylcholine is a depolarizing neuromuscular blocking agent. When succinylcholine binds to the postjunctional nicotinic cholinergic receptor, postjunctional membrane depolarization occurs. This rapid depolarization also causes a leakage of potassium that can cause serum potassium levels to increase from 0.5 to 1.0 mEq/L. Recovery from neuromuscular blockade occurs when succinylcholine diffuses out of the neuromuscular junction down a concentration gradient as the plasma concentration decreases. Succinylcholine is metabolized by a circulating glycoprotein called plasma cholinesterase (pseudocholinesterase). Pseudocholinesterase, which is synthesized in the liver and circulated in the plasma, rapidly hydrolyzes succinylcholine into choline and succinate. The initial metabolite of succinylcholine, succinylmonocholine, causes bradycardia in infants and children through the stimulation of sinus node muscarinic receptors. Succinylcholine cannot be reversed by neostigmine.

2. C

   The activity of non-depolarizing neuromuscular drugs can be enhanced or diminished by certain agents. Enhanced activity is seen with magnesium, volatile anesthetics, local anesthetics, antiarrhythmic drugs, and aminoglycosides. Drugs that diminish the effect of non-depolarizing neuromuscular blockers include steroids, calcium, and phenytoin.

3. A

   Cisatracurium is degraded by Hofmann elimination, which is a process of spontaneous degradation at physiological pH in the blood. Its duration of action is not significantly affected by liver or kidney dysfunction. Pancuronium action is prolonged in renal and hepatic impairment. It is partly de-acylated in the liver to a 3-hydroxy metabolite which is half as potent as pancuronium. A major portion of pancuronium and its active metabolite are excreted in the urine making its duration of action significantly prolonged in patients with renal failure. Rocuronium is metabolized in the liver and excreted in the bile and would have a prolonged action in patients with liver dysfunction.

Vecuronium is metabolized in the liver to active metabolites and is excreted in the bile and urine and would also have prolonged action in patient with both kidney and liver failure or dysfunction. Tubocurarine is excreted unchanged in the urine and the bile and would therefore have a prolonged duration of action in patients with kidney or liver dysfunction.

4. D
Sugammadex forms a complex with the non-depolarizing neuromuscular blocking agents rocuronium and vecuronium. It does not form a complex with benzylisoquinoline neuromuscular blockers. High doses of sugammadex can be used to reverse a deep neuromuscular blockade with either rocuronium or vecuronium. 16 mg/kg of sugammadex can reverse neuromuscular blockade after high doses of rocuronium (1.2 mg/kg) given for a rapid sequence induction when no twitches are present on train-of-four stimulation. Edrophonium and atropine would not be appropriate reversal agents for pancuronium. Edrophonium and atropine have short half-lives, while pancuronium is a long-acting neuromuscular blocker with a much longer half-life. When the short-lived effects of edrophonium and atropine have worn off, the patient would be in danger of becoming re-paralyzed with pancuronium.

5. B
Differences in regional blood flow have an influence in the recovery from neuromuscular blockade. The muscles that have the highest amount of regional blood flow recover the fastest. The diaphragm and laryngeal muscles have rapid recovery from neuromuscular blockade due to high amounts of regional blood flow to these muscles. The masseter and adductor pollicis muscles have a relatively lower amount of regional blood flow and therefore, have a much slower recovery time.

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Renal and Electrolyte

Contents

Overview, Structure, and Function of the Nephron

George J. Schwartz and Megan Rashid

Contents

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Learning Objectives

- Understand the structure and function of the nephron and know the roles of the glomerulus, proximal tubule, loop of Henle, distal tubule, and collecting duct on urine formation and composition.
- Understand the basis for the concentration of urine (countercurrent).
- Understand the energy requirements of the normal kidney and how this makes particular areas (functions) "ischemia sensitive"; understand the potential effects of renal ischemia.
- Understand the regulation of renal blood flow.
- Understand the role of the kidney in the maintenance of circulating blood volume; understand that "renal maintenance" of circulating blood volume is slower and longer-lived than the vasoconstriction associated with a baroresponse.
- Understand the roles of the renin/angiotensin system, atrial natriuretic peptide, and antidiuretic hormone (ADH) in maintaining circulating blood volume and electrolyte (sodium) homeostasis; know the renal sites of action of these systems.
- Understand the renal role in acid-base homeostasis and the major potential sites and mechanisms of breakdown of these functions.
- Understand the age-related changes in normal renal function and biochemical markers of renal function.
- Understand the actions of commonly used diuretics on the renal "unit".

At birth, the kidneys measure about 4–5 cm. Growth, usually evaluated by ultrasound, is rapid in the first 2 years and then slows until an adult size about 12 cm is reached in adolescence.

In a term infant at birth, the kidneys measure about 4–5 cm. They experience a period of rapid growth in the first 2 years. Thereafter, growth slows to 2–3 mm/year until an adult size of about 12 cm is reached in adolescence. Renal ultrasound is commonly used to evaluate the size and interval growth of the kidneys (Fig. 29.1). There is wide variation in normal kidney size. The left kidney is usually larger than the right, but the plots generally do not distinguish the two sides. Renal length has often been plotted as a function of age (Table 29.1).

29.1 Structure of the Nephron

The functional unit of the kidney is the nephron, which is comprised of the glomerulus and the tubule. The glomerulus acts as a filter, while the ultrafiltrate is modified in the tubule to produce urine.

The functional unit of the kidney is the nephron (Fig. 29.2), which is comprised of the glomerulus (Figs. 29.3 and 29.4) and the tubule. The tubule can be further divided into the proximal tubule, the loop of Henle, the distal tubule, and the collecting duct. The glomerulus functions as a filter. Blood enters via the afferent arterioles in the vascular pole of the glomeruli, which drain into a capillary bed within Bowman's capsule. The capillary wall acts as a barrier as an ultrafiltrate is formed by movement of fluid out of the capillaries into Bowman's space. There are three layers of the capillary wall – the fenestrated endothelial cell (which lines the lumen of the capillary), the glomerular basement membrane, and the epithelial cell (podocyte). These three layers form a barrier for both size and charge to prevent the loss of large, negatively charged molecules. The epithelial cells are connected to the glomerular basement membrane by foot processes. In nephrotic syndrome (Fig. 29.4), loss of the foot processes can lead to leaking of albumin, which normally remains in the capillary due to its large size and negative charge. Once the ultrafiltrate is formed in Bowman's space, it leaves the glomerulus through the urinary pole and travels into the proximal tubule. The blood remaining in the glomerular capillary bed is drained by the efferent arterioles and returned to the systemic circulation. Within the tubule, the ultrafiltrate is modified in a highly regulated process to produce urine that varies to maintain the extracellular environment within the body.

The urine can be modified within the tubule in a number of ways, with each segment making a distinctive contribution. At the beginning of the tubule, the urine is an ultrafiltrate which is similar to plasma in electrolyte composition and osmolality. The removal of a substance from the ultrafiltrate within the tubule is known as reabsorption, while secretion is the addition of a substance to the ultrafiltrate. Excretion is the elimination of water and solutes from the body through removal in the form of urine. In order for a substance to be reabsorbed, it must reach the peritubular capillary by either travel through or between the epithelial cells. With intracellular transport, transport occurs across the luminal membrane, and in order to exit the cell, the substance must then pass through the basolateral membrane to reach the interstitium. From there, it can be taken up into the peritubular capillaries and returned to the circulation. Each section of the tubule plays a distinctive role in modification of the urine, with varying permeabilities to water and a variety of channels and transporters to facilitate movement of solutes.

The major roles of each segment of the tubule are outlined in Table 29.2. The proximal tubule is responsible for the reabsorption of the bulk of the filtered sodium and water, in addition to much of the filtered bicarbonate, protein, glucose, and electrolytes. In the next segment of the nephron (Fig. 29.3), the loop of Henle, sodium is reabsorbed in excess of water, generating a hypotonic urine and a hypertonic interstitium which is necessary for urinary concentration. The distal tubule is a major site of regulated calcium excretion, under the influence of parathyroid hormone and possibly calcitriol, and is the site of the thiazide-sensitive NaCl transporter. The collecting tubule is respon-

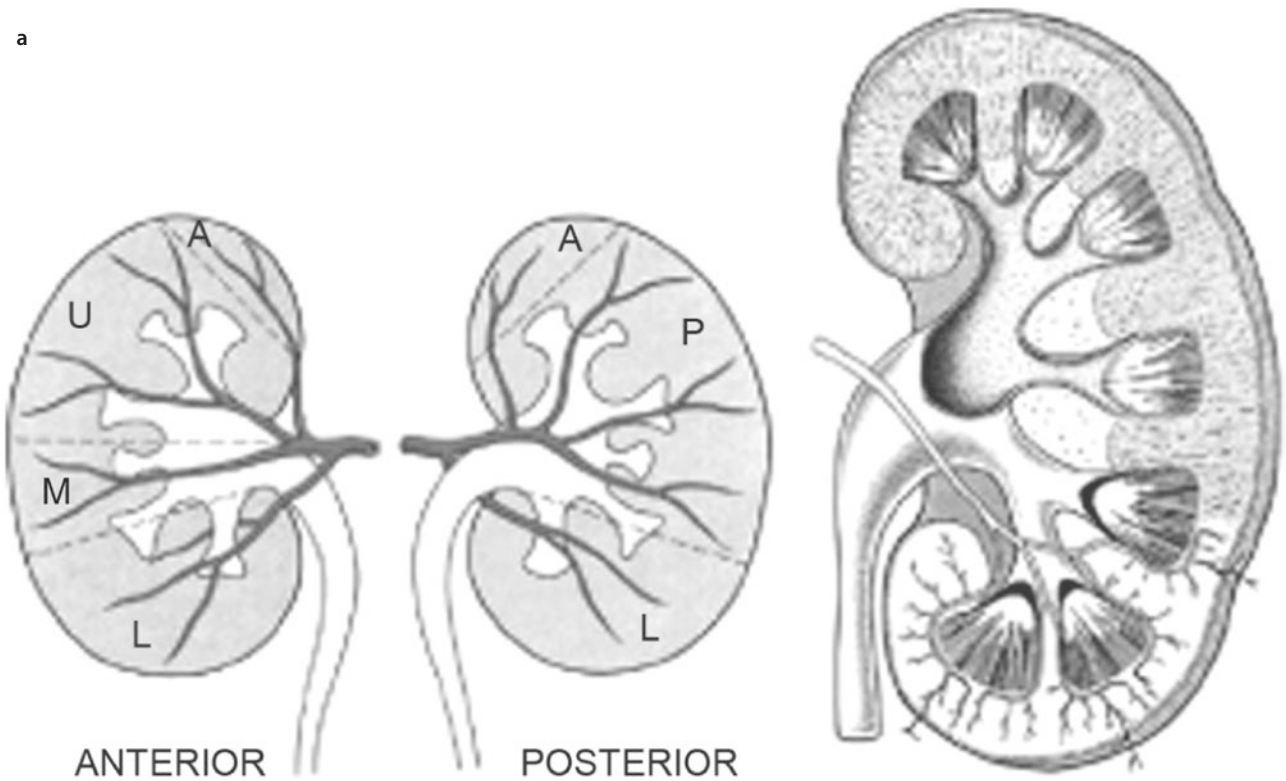

Fig. 29.1 Renal anatomy. **a** Schematic of renal anatomy highlighting the arterial blood flow. **b** Ultrasound (US) of a neonatal kidney: more spherical shape, broad corticomedullary complex with echogenic cortex and prominent corticomedullary differentiation, no or minimal central sinus echoes, echogenic papillae, and fetal lobulation. **c** US appearance of the kidney in an adolescent for comparison

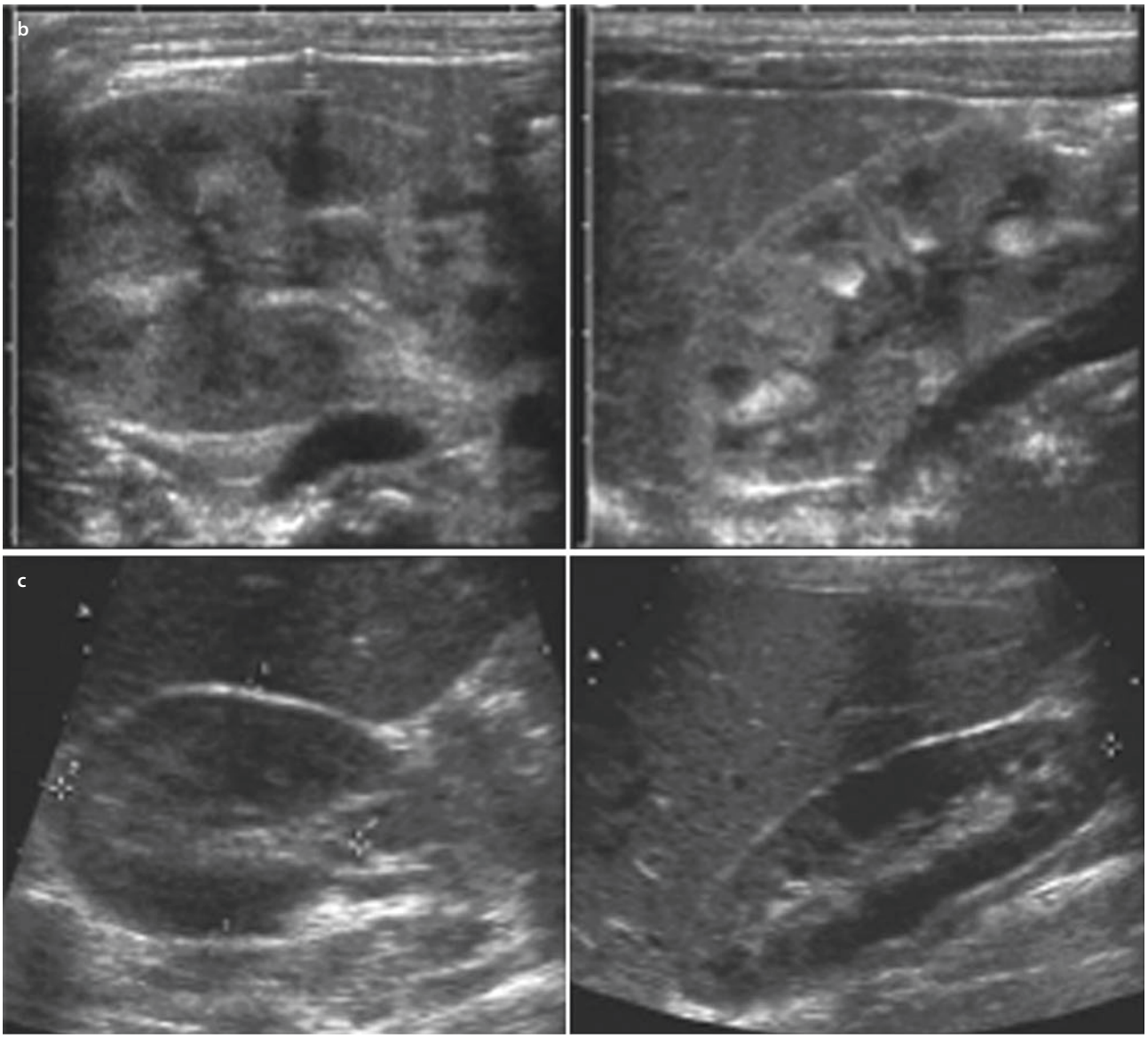

Fig. 29.1 (continued)

The clinical manifestations of Fanconi syndrome, generalized proximal tubule dysfunction, include acidosis, polyuria, hypophosphatemia, hypokalemia, glucosuria, and aminoaciduria.

sible for the final adjustments to the urine, with multiple important roles including antidiuretic hormone (ADH)-mediated water reabsorption and aldosterone-mediated regulation of proton and potassium secretion and sodium reabsorption.

In a normal adult, 130–180 L of ultrafiltrate are formed daily in the glomeruli. The proximal tubule is able to reduce this ultrafiltrate volume significantly and is responsible for the recovery of a number of solutes, including about 65% of the filtered sodium and water. Sodium is transported across the basolateral membrane to the peritubular capillary by active transport via Na^+-K^+ATPase (Fig. 29.5). This sodium extrusion creates a favorable electrochemical gradient for sodium to enter the cell through the apical membrane from the ultrafiltrate. Other solutes, such as glucose and amino acids, are reabsorbed almost completely through cotransporters that are linked to sodium reabsorption, called secondary active transport. The removal of solutes results in creation of an osmotic gradient which leads to passive water reabsorption

Table 29.1 Sonographic length of kidneys in children

Age (years)	Mean renal length (cm)	SD/N
0	4.48	0.31/10
0.5	6.15	0.67/20
1.5	6.65	0.54/28
3.5	7.36	0.64/30
5.5	8.09	0.54/30
8.5	8.90	0.88/18
10.5	9.17	0.82/28
12.5	10.42	0.87/18
14.5	10.05	0.62/14
16.5	10.04	0.86/10
18.5	10.81	1.13/8

SD standard deviation, *N* the number assessed for each age category
Data from Rosenbaum DM, Korngold E, Teele RL. Sonographic assessment of renal length in normal children. AJR. 1984;142:467–9

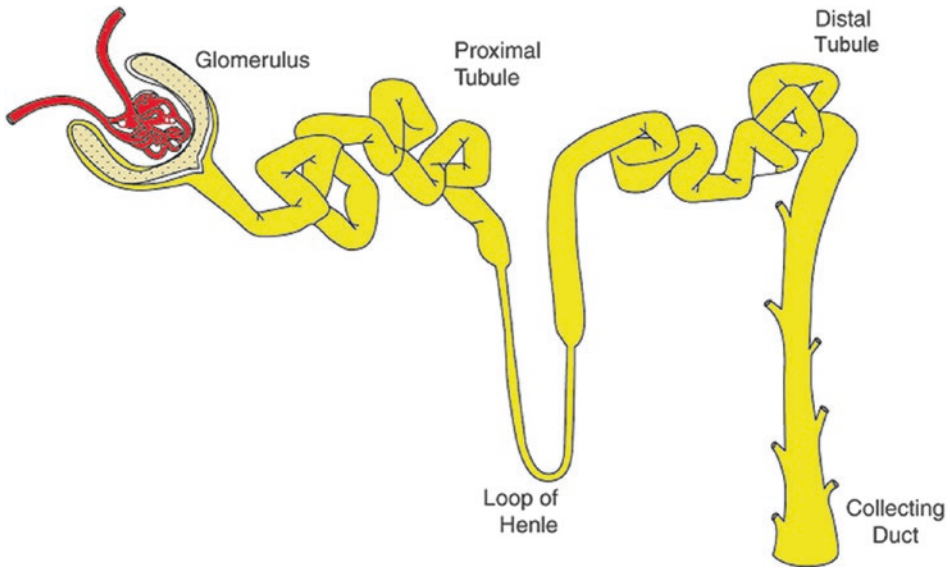

Fig. 29.2 Structure of the nephron, the smallest unit of the kidney, demonstrating the contiguous segments

across the highly permeable proximal tubule cells. The proximal tubule is also the major site for bicarbonate recovery, with reabsorption of approximately 80% of filtered bicarbonate. In addition, although urinary acidification occurs in the collecting tubule, the process is dependent on ammonium which is produced in the proximal tubule cells. The proximal tubule also plays an important role in the reabsorption of potassium, phosphorus, calcium, magnesium, urea, and uric acid. The latter is also secreted in the late proximal tubule. The importance of the proximal tubule is evident in Fanconi syndrome, a clinical state in which there is generalized proximal tubular dysfunction. Fanconi syndrome can be due to inherited conditions, or can be acquired, such as due to chemotherapy with cisplatin or ifosfamide. The clinical manifestations of Fanconi syndrome – acidosis, polyuria, hypophosphatemia, hypokalemia, glu-

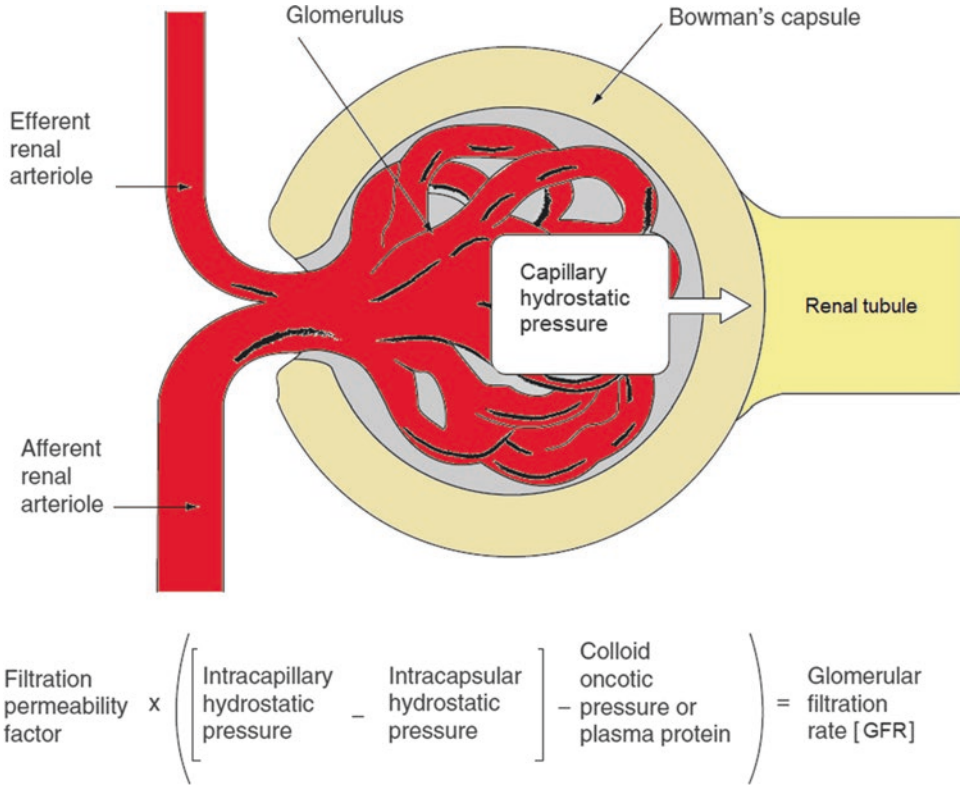

Fig. 29.3 The glomerular apparatus is a network of capillaries originating from the afferent arteriole and surrounded by an extension of a basement membrane from the proximal tubule called *Bowman's capsule*. The rate of urine formation, i.e., glomerular filtration rate (GFR) or ultrafiltration, depends on hydraulic permeability of the glomerular capillaries and net ultrafiltration pressure across the capillary wall. These Starling forces govern glomerular filtration. In addition to being dependent on hydraulic and oncotic pressures within the glomerular capillary, urine formation is also influenced by local and systemic neurohumoral influences, exogenous administration of diuretics, and an intact kidney-ureter-bladder feedback loop

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cosuria, and aminoaciduria – highlight some of the major functions of the proximal tubule.

Isoosmotic fluid leaving the proximal tubule enters the loop of Henle. The loop of Henle is divided into three segments: the thin descending limb, the thin ascending limb, and the thick ascending limb. In the loop of Henle, 25–35% of the filtered sodium chloride is reabsorbed and passive reabsorption of calcium and magnesium occurs. The main function, however, is to generate a hyperosmolar interstitium through reabsorption of sodium in excess of water in the thick ascending limb, which is impermeable to water. This is powered by the Na^+-K^+ATPase in the basolateral surface and is facilitated by passive entry of sodium, chloride, and potassium through the bumetanide-sensitive Na^+-K^+-$2Cl^-$ carrier in the luminal membrane (Fig. 29.6). Loop diuretics compete for the chloride channel in the Na^+-K^+-$2Cl^-$ carrier, resulting in inhibition of sodium and potassium reabsorption. The removal of sodium, chloride, and potassium in the absence of water reabsorption leads to a hypertonic interstitium and results in hypotonic urine leaving the loop of Henle (Fig. 29.7). As a result of the hypertonic interstitium, the descending limb of the loop of Henle, which is permeable to water, is able to passively reabsorb water. This is known as countercurrent multiplication.

Thiazides increase the potency of loop diuretics by blocking the flow-dependent increase in sodium reabsorption in the distal tubule.

The distal tubule reabsorbs about 5% of the filtered sodium mostly through the thiazide-sensitive Na^+-Cl^- cotransporter. Sodium reabsorption in the loop of Henle and the distal tubule is flow dependent, so the capacity to reabsorb sodium can increase if there is increased flow. If sodium reabsorption is blocked, such as by a loop diuretic (e.g., furosemide), then sodium reabsorption in the distal tubule is augmented. Blocking sodium reabsorption in the distal tubule with a thiazide diuretic can enhance this effect, resulting in a more potent diuresis when a thiazide is used in conjunction with a loop diuretic.

Whereas some water is reabsorbed in the descending loop of Henle, the major site of countercurrent multiplication is in the collecting duct. Although

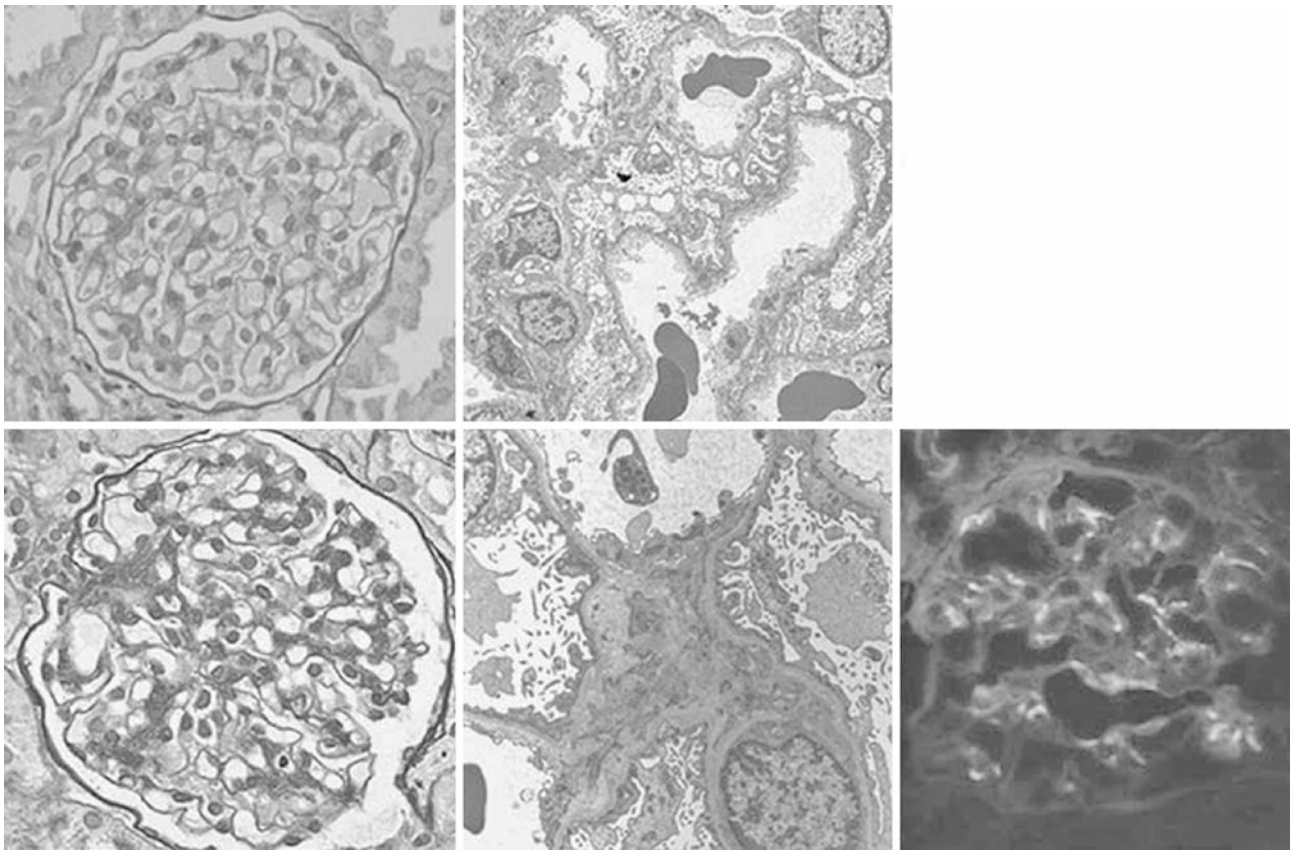


Fig. 29.4 The renal pathologic findings of minimal-change nephrotic syndrome. The first biopsy performed at age 4 years revealed a normal-looking glomerulus (light microscope, upper left panel, PAS stain, ×400) and wide foot process effacement (electron microscope, upper middle panel, ×2500). The second biopsy performed at age 11 years revealed segmental mesangial cell proliferation (light microscope, lower left panel, PAS stain, ×400), mesangial electron-dense deposits and widely effaced foot processes (electron microscope, lower middle panel, ×4000), and mesangial IgA deposition (immunofluorescent microscope, lower right panel, ×400)

The removal of sodium in excess of water in the loop of Henle allows for generation of a hypertonic interstitium which is necessary for urinary concentration by countercurrent multiplication.

the urine entering the collecting duct is hypotonic, the ultimate concentration of the urine is determined by the permeability of the collecting duct to water. This is regulated by antidiuretic hormone (ADH), which controls the insertion of aquaporin-2 water channels into the luminal membrane of the collecting duct to allow equilibration with the interstitium. In a state of high ADH, the collecting duct will be highly permeable to water. Through the countercurrent mechanism, with a hypertonic interstitium generated by the loop of Henle, water diffuses into the interstitium and is reabsorbed, resulting in a concentrated urine. In humans, this process is so efficient that a urinary concentration of 1000–1200 mOsm/kg can be achieved. If serum ADH levels are low, such as in states of high water intake, the collecting tubule will be relatively impermeable to water, resulting in a dilute urine with osmolality as low as 30–50 mOsm/kg. Again, the efficiency of the process is highlighted by the fact that an individual can drink more than 10 L of fluid a day and still maintain a normal serum osmolality. Thus, the generation of concentrated urine requires a hypertonic interstitium and ADH-induced water channels (▶ Box 29.1). In order for dilute urine to be generated, there must be a state of low water permeability in the collecting tubule and adequate NaCl reabsorption in the loop of Henle. The collecting tubule, in addition to the role it plays in urinary concentration, is also the main site for the regulation of potassium.

Table 29.2 Primary functions of each segment of the nephron

Nephron segment	Function
Glomerulus	Formation of ultrafiltrate
Proximal tubule	65% of filtered sodium and 55–60% of water reabsorbed
	80% of filtered bicarbonate recovered
	Almost all glucose, organic solutes, and amino acids reabsorbed
	Potassium, phosphorus, calcium, magnesium, urea, and uric acid reabsorbed; uric acid also secreted in the late proximal tubule
Loop of Henle	25–35% of filtered NaCl reabsorbed (in excess of water, resulting in hypertonic medullary interstitium, necessary for countercurrent multiplication)
	Major site of magnesium reabsorption
Distal tubule	Regulates urinary calcium excretion
	5–8% of filtered sodium reabsorbed
Collecting duct	5–7% of filtered sodium reabsorbed through luminal channel (ENaC) Presence or absence of ADH-induced water channels determines urine concentration.
	Aldosterone-mediated potassium and proton secretion and sodium reabsorption Flow-mediated potassium secretion (ROMK plus maxi-K channel)
	Acidification through titration of urinary ammonia

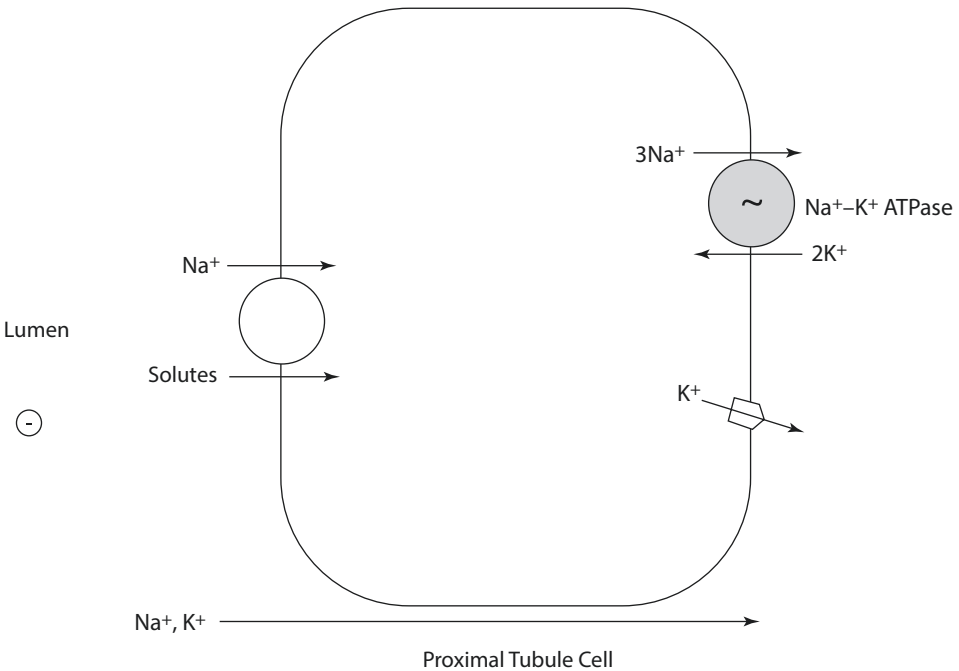


Fig. 29.5 Proximal tubule cell, simplified diagram demonstrating sodium-dependent cotransport of solutes, paracellular cation flow, and basolateral Na^+-K^+-ATPase

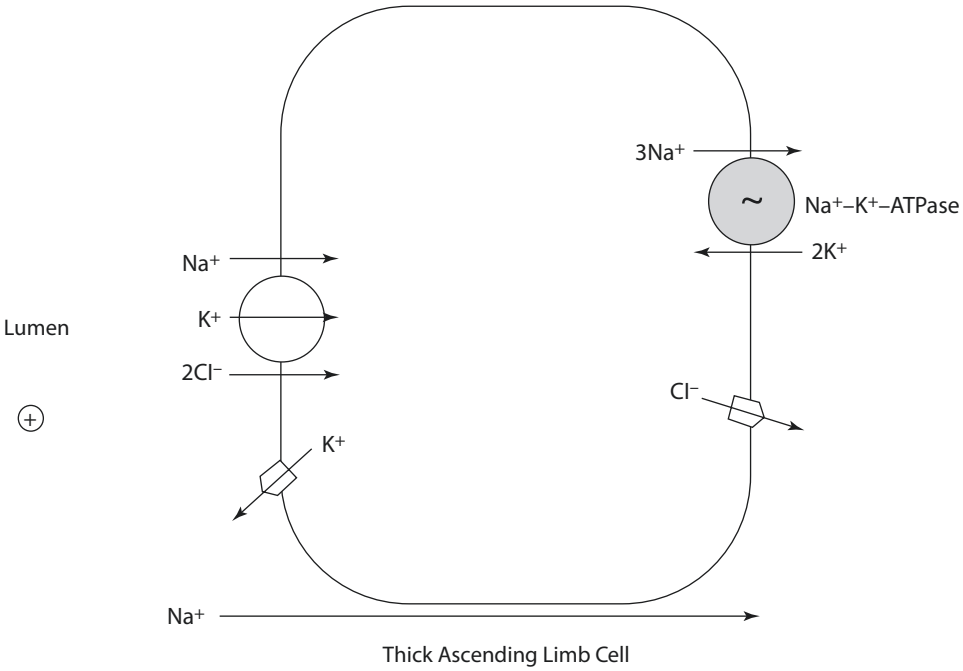


Fig. 29.6 Thick ascending limb cell, simplified diagram, demonstrating apical Na^+-K^+-$2Cl^-$ cotransporter, ion channels, and basolateral Na^+-K^+-ATPase

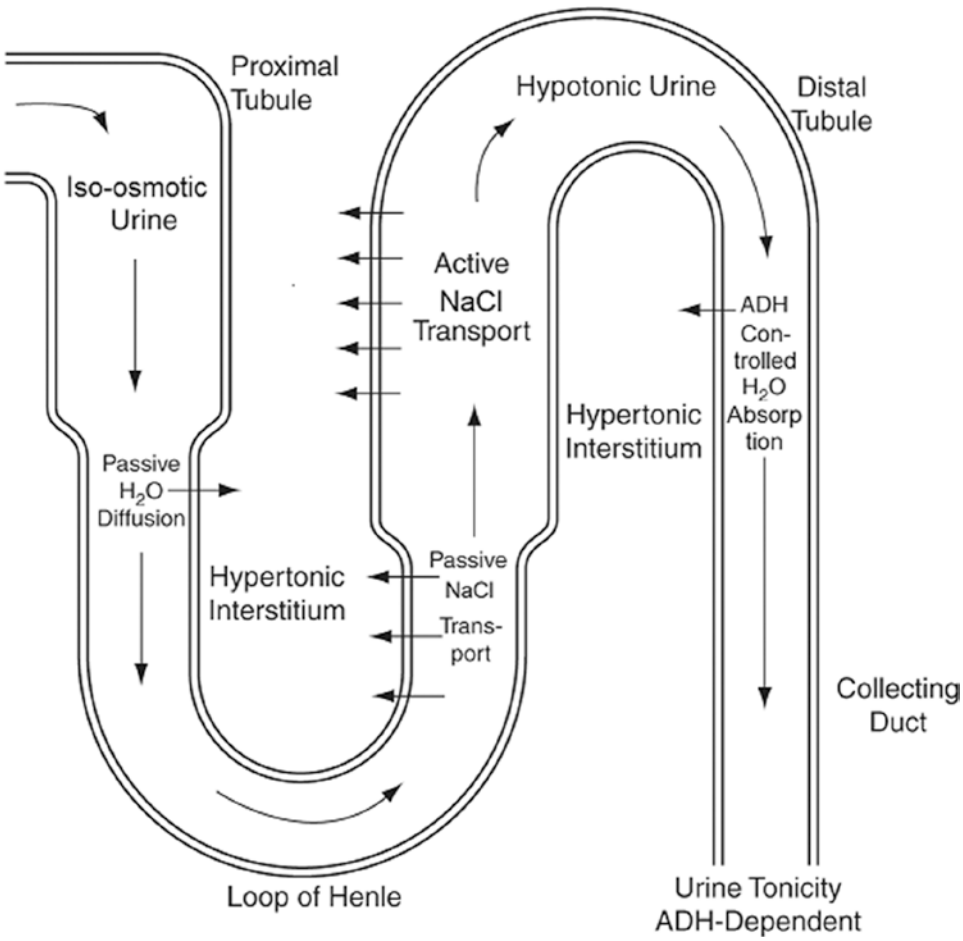


Fig. 29.7 The drawing depicts countercurrent multiplication by the kidney illustrating the relative tonicity along the nephron as gradients are generated by the thick ascending limb cells

Box 29.1 Factors Necessary to Generate a Concentrated or Dilute Urine

1. Factors required for the formation of a concentrated urine:
   (a) Hypertonic interstitium, generated by the loop of Henle
   (b) Presence of ADH-induced water channels in the collecting tubule apical membrane
2. Factors required for the formation of a dilute urine:
   (a) Reabsorption of NaCl in excess of water in the loop of Henle
   (b) Absence of ADH-induced water channels in the collecting tubule apical membrane
   (c) Normal glomerular filtration rate

29.2 Regulation of Renal Blood Flow

Blood is supplied to each kidney at the hilum by the renal artery, which is usually single, but can be duplicated. The renal artery branches into segments which supply the interlobar arteries (Fig. 29.1). These segments are end arteries. Thus, if the blood flow to any segment is compromised, there are no alternate sources of blood supply. The interlobar arteries travel to the arcuate arteries, which curve parallel to the surface of the kidney at the corticomedullary junction. The interlobular arteries arise from the arcuate arteries and traverse outward within the cortex toward the surface. From these, the afferent arterioles supply the glomerular capillary bed, which is then drained by the efferent arterioles. In the cortex, the efferent arterioles supply the peritubular capillaries, which surround the tubules. In contrast, in the medulla, the efferent arterioles give rise to the vasa recta, which supply the interstitium and run in close proximity to the loop of Henle. The venous drainage of the kidney follows a similar distribution to that of the arterial supply.

29.2.1 Regulation of Renal Blood Flow, Determinants of Glomerular Filtration Rate

The combined ultrafiltrate formed by all functional glomeruli is the total GFR. Total GFR is sometimes expressed as mL/min in adults, but in most adults and all children, it is normalized by surface area and expressed as mL/min per 1.73 m^2.

Urine is formed as an ultrafiltrate of renal plasma which exits the glomerular capillaries and crosses the semipermeable glomerular basement membrane to enter Bowman's space. The rate of production of ultrafiltrate by each nephron is known as the single nephron glomerular filtration rate (GFR). The combined ultrafiltrate formed by all functional glomeruli is the total GFR. Total GFR is sometimes expressed as mL/min in adults, but in most adults and in all children, it is normalized by surface area and expressed as mL/min per 1.73 m^2.

GFR is determined by Starling's law, which states that the flow of substance across a permeable surface is determined by the permeability of the surface, the area available for filtration, and the pressure difference between the two compartments. The pressure difference is determined by the gradients of hydraulic pressure (P) and oncotic pressure (π) across the capillary membrane (Fig. 29.8). The pressure within the glomerular capillary (P_{gc}) is determined both by the systemic perfusion pressure and by the resistance within the afferent and efferent arterioles. The afferent arteriole resistance modifies the systemic perfusion pressure, decreasing it with vasoconstriction and hence lowering the P_{gc}. In contrast, as the renal plasma exits the capillary, constriction of the efferent arteriolar will provide resistance to outward flow and cause increasing pressure within the capillary.

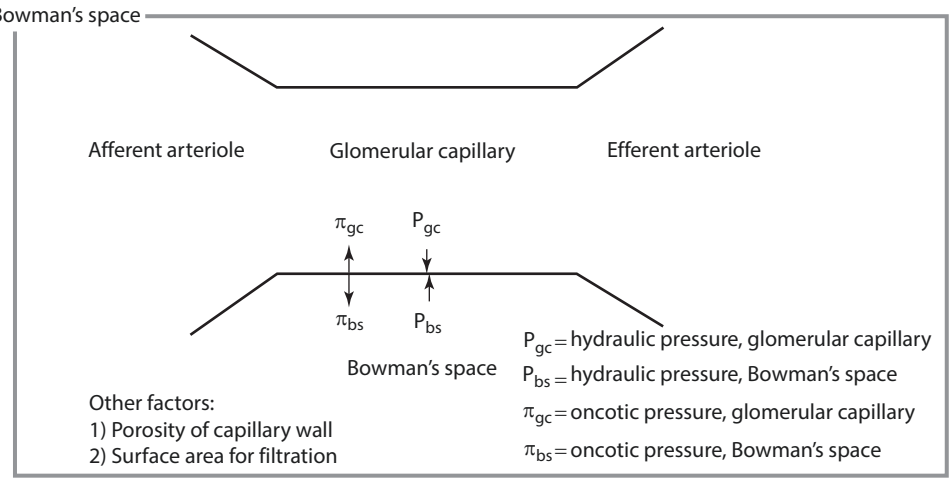


Fig. 29.8 The diagram depicts factors that affect glomerular filtration rate, particularly the balance between hydraulic and oncotic pressures

$$\text{RPF} = \frac{\text{Pressure}}{\text{Resistance}} = \frac{\text{Renal arterial pressure} - \text{renal venous pressure}}{\text{Renal vascular resistance}}$$

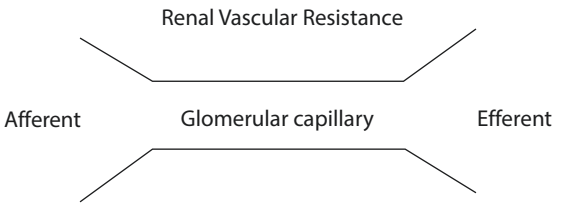


Fig. 29.9 Diagram depicting factors that influence renal plasma flow (*RPF*). Renal plasma flow is affected primarily by arteriolar tone. An increase in the tone at either end of the glomerular capillary will raise vascular resistance and decrease renal plasma flow. Alterations in efferent (but not afferent) arteriolar tone will change the ratio of glomerular filtration rate to renal plasma flow

Under normal circumstances, the surface area and permeability of the capillary wall are relatively stable and, thus, do not cause changes in GFR. However, disease states can affect the capillary wall, leading to large decrements in GFR. For example, in many glomerular diseases, inflammation or destruction of glomeruli decreases the surface area available for filtration, resulting in a reduced GFR. Similarly, while the hydraulic pressure within the glomeruli is generally stable and, hence, plays little role in fluctuations in the GFR, this can change when there is obstruction to urine flow. For example, ureteral obstruction due to compression from an abdominal mass causes increased pressure in the proximal ureter. This pressure is transmitted to the glomerulus, increasing the hydraulic pressure in Bowman's space (P_{bs}) and decreasing GFR.

Renal plasma flow is determined by the ratio of the pressure of the plasma to the resistance of the blood vessels (Fig. 29.9). The pressure is the difference between the aortic pressure and the venous pressure. Thus,

$$\text{RPF} = \Delta P / \text{R} = \frac{\left(\text{renal arterial pressure} - \text{renal venous pressure}\right)}{\text{renal vascular resistance}}$$

The renal vascular resistance is a function of the resistance in both the afferent and efferent arteriole as the two are in series, and hence, the total resistance will increase with vasoconstriction of either vessel. GFR and renal plasma flow (RPF) are regulated in parallel at the afferent arteriole, but reciprocally at the

efferent arteriole. For example, with efferent arteriole vasoconstriction, there is a decrease in RPF but a potential increase in the pressure of the glomerular capillary and in the GFR.

The relationship between RPF and GFR is complex. The GFR is determined by the forces across the capillary wall and is not directly affected by RPF. However, along the length of the capillary, protein-free fluid is removed, increasing the plasma protein concentration and hence the plasma oncotic pressure (π_{gc}). As π_{gc} increases, there will be less filtration across the capillary wall, until at a certain π_{gc}, the rate of filtration falls to zero. This is known as filtration equilibrium. At the point at which filtration equilibrium is reached, no further ultrafiltrate can be formed at the same renal plasma flow. Thus, the GFR may be limited by the RPF, and only with increasing blood flow can the GFR be increased.

Since both GFR and RPF are affected by systemic blood pressure, which fluctuates throughout the day, it might be expected that there would be parallel variation in GFR and RPF. This does not occur, however, due to autoregulation within the kidney. Autoregulation refers to the ability of the kidney to maintain RPF and GFR over a wide range of blood pressures. In adults, the kidney can maintain GFR and RPF within a narrow range for varying systemic blood pressures as long as the mean arterial pressure (MAP) is greater than 70 mm Hg. RPF and GFR will fall with any further reduction in systemic pressure, and if the MAP falls below 40–50 mm Hg in the adult, no ultrafiltrate is formed.

Autoregulation refers to the ability of the kidney to maintain RPF and GFR over a wide range of blood pressures.

Autoregulation of blood flow is not unique to the kidney, but can be found in the vascular beds of the brain and heart as well. Kidneys that have been isolated and denervated maintain the ability for autoregulation. Autoregulation is accomplished at the level of a single nephron by both a myogenic reflex and tubuloglomerular feedback (Fig. 29.10). When there is an increase in pressure in the arterioles, there is an immediate myogenic response which leads to vasoconstriction in the afferent arteriole, preventing increased renal plasma flow and maintaining glomerular capillary pressure and thus GFR. Conversely, with a decrease in blood pressure, the afferent arteriolar vasodilation protects GFR from falling. In addition, tubular glomerular feedback occurs when increased tubular flow rate leads transiently to increased chloride delivery to the thick ascending limb in the loop of Henle. The increased chloride concentration is sensed by the cells of the macula densa. The macula densa then stimulates afferent arteriolar vasoconstriction. The constriction in the afferent arteriole lowers the renal perfusion pressure, and therefore RPF, and maintains a constant glomerular capillary pressure resulting in maintenance of the GFR. Loop diuretics can impair this tubular glomerular feedback.

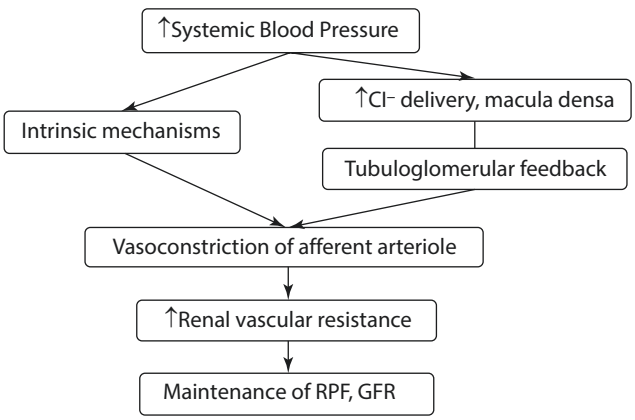


Fig. 29.10 Diagram depicting autoregulation illustrating the maintenance of glomerular filtration rate (*GFR*) and renal plasma flow (*RPF*) after an increase in arterial pressure. An opposite adaptation would occur with a small decrease in arterial pressure

In addition to the role they play in tubuloglomerular feedback, the macula densa cells mediate renin release by the juxtaglomerular cells. Production of angiotensin II (AII) is catalyzed by renin, which is released in response to a fall in perfusion pressure (Fig. 29.11). AII has numerous effects which are discussed later in the chapter and which have variable effects on GFR. However, AII can play an important role in maintaining GFR in states of hypovolemia. AII causes vasoconstriction in both the afferent and efferent arterioles. However, there is greater constriction in the efferent than the afferent arterioles resulting in an increase in pressure within the glomerular capillary, maintaining GFR even in the face of decreased perfusion pressure. This can be clinically important for patients taking angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor antagonists. Such agents block AII action, which can lead to a fall in GFR in states of hypotension, heart failure, or renal artery stenosis. The effects of different mediators on GFR and RPF are detailed in Table 29.3.

29.3 Determination of Glomerular Filtration Rate (GFR)

The proportion of RPF that crosses the basement membrane to form an ultrafiltrate is known as the filtration fraction (FF):

$$FF = GFR / RPF$$

Substances that are filtered into the urine or secreted in the tubules are removed from the blood and excreted in the urine. The clearance of a substance is the calculated volume of plasma per unit time (flow rate in mL/min) from which a substance would have to be completely removed to account for its rate of excretion in the urine. For a substance that is freely filtered and not absorbed or secreted, such as inulin, the clearance is equal to the GFR. This is illustrated in Fig. 29.12, which is a schematic representation of inulin being cleared from plasma. Plasma is delivered as RPF with a concentration of inulin (P_{in}) (mg/mL).

The clearance of a substance is the volume of plasma per unit time from which a substance would have to be totally removed to account for the rate of excretion in the urine. For a substance that is freely filtered and not absorbed or secreted, such as inulin, the clearance is equal to the GFR.

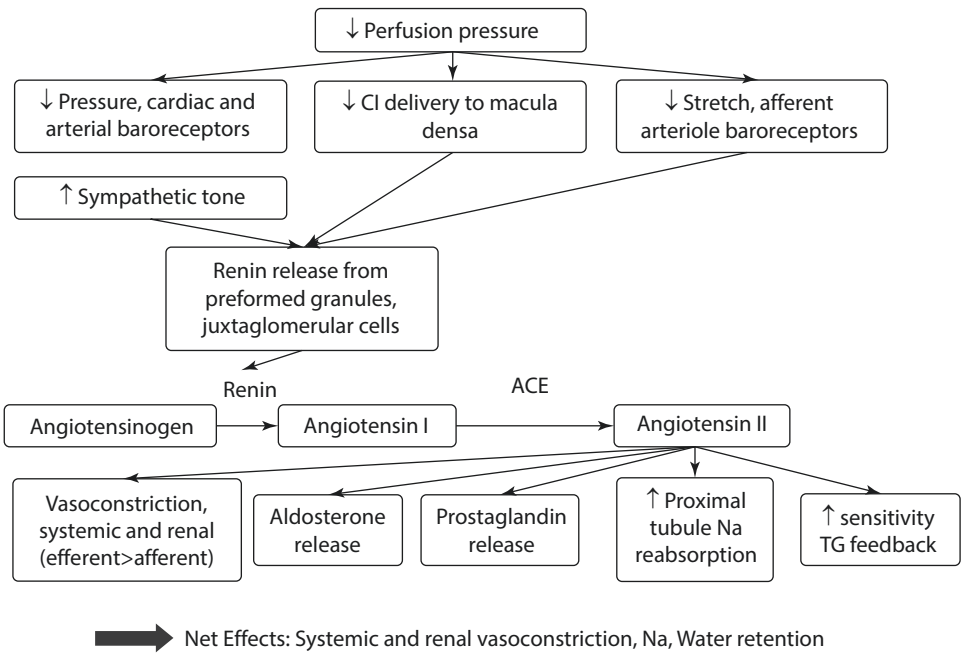


Fig. 29.11 Diagram depicting the renin-angiotensin-aldosterone axis response to a decrease in perfusion pressure. *ACE* angiotensin converting enzyme, *TG* tubuloglomerular feedback

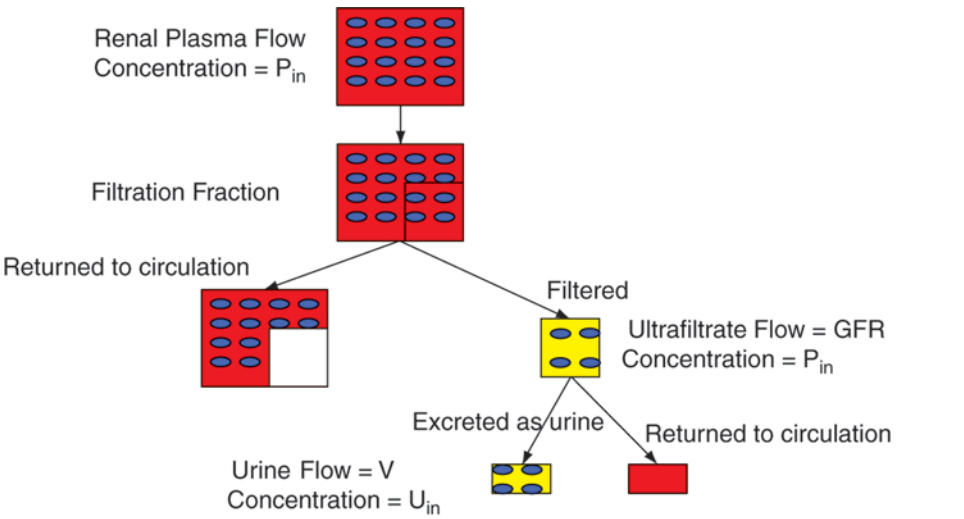
Table 29.3 Effect of different mediators on GFR and RPF

	Afferent arteriole resistance	Efferent arteriole resistance	Renal plasma flow	Glomerular filtration rate
Sympathetic nervous system activation	↑↑	↑	↓	↓
Dopamine (low dose)[a]	↓	↓	↑	↑
Dopamine (high dose)[b]	↑	↑	↓	↓
Epinephrine	↑	↑	↓	↓
Norepinephrine	↑	↑	↓	↓
Prostaglandins (PGE_2 & PGI_2)	↓	↓ (?)	↑	↑
NSAIDS	↑↑	↑	↓	↓
Angiotensin II	↑	↑↑	↓	Variable
ACE inhibitors/ARBs	↓	↓↓	↑	Variable, usually decreased

PGE_2 prostaglandin E_2, *PGI_2* prostaglandin I_2, *NSAIDS* nonsteroidal anti-inflammatory drugs, *ACE* angiotensin converting enzyme, *ARBs* angiotensin II receptor blocker

[a]Low dose indicates a dopamine infusion rate of <5 mcg/kg/min

[b]High dose indicates a dopamine infusion rate of ≥8 mcg/kg/min



Flow rate ultrafiltrate × Concentration ultrafiltrate = Flow rate urine × Concentration urine

$$GFR \times P_{in} = V \times U_{in}$$

$$GFR = V \times U_{in} / P_{in}$$

Fig. 29.12 The clearance of inulin. The clearance of inulin remains the gold standard for the measurement of glomerular filtration rate (*GFR*). This figure demonstrates that clearance refers to that volume of plasma from which the inulin is removed by renal excretion. Plasma is delivered as renal plasma flow with a concentration of inulin (P_{in}) (mg/mL). The fraction of the renal plasma which forms ultrafiltrate is the GFR, which has the same concentration of inulin as the plasma (P_{in}) since it is freely filtered. The urine is then formed with a flow rate of V (mL/min) and an inulin urine concentration (U_{in}) (mg/mL). By the law of mass balances, the inulin which is freely filtered is entirely excreted. The GFR can then be determined using the equations at the bottom of the figure

The fraction of the renal plasma which forms ultrafiltrate is the GFR, which has the same concentration of inulin as the plasma (P_{in}) since it is freely filtered. The urine is then formed with a flow rate of V (mL/min) and an inulin urine concentration (U_{in}) (mg/mL). By the law of mass balances, the inulin which is freely filtered is entirely excreted. Thus,

$$\text{Flow rate of ultrafiltrate} \times \text{Concentration of ultrafiltrate} = \text{Flow rate of urine} \times \text{Concentration of urine}$$

$$\text{GFR} \times P_{in} = V \times U_{in}$$

If the concentrations of inulin in the blood and urine are known, and the volume of urine (V) per day is known, the equation can be used to calculate GFR:

$$\text{GFR} = \frac{V\left(\text{mL/min}\right) \times U_{in}\left(\text{mg/mL}\right)}{P_{in}\left(\text{mg/mL}\right)}$$

In children and most adults, the GFR is normalized by body surface area (BSA). Thus, the calculation can be modified as follows:

$$\text{GFR}\left(\text{mL/min/1.73m}^2\right) = \frac{V\left(\text{mL/min}\right) \times U_{in}\left(\text{mg/mL}\right) \times 1.73}{P_{in}\left(\text{mg/mL}\right) \times \text{BSA}\left(\text{m}^2\right)}$$

29.3.1 Changes in GFR with Age

The infant has a relatively low GFR, immature tubular function, and limited ability to adapt in times of physiologic stress.

In the human embryo, the primitive kidneys, the mesonephric ducts, begin to develop at about 24 days. They produce small amounts of urine between 6 and 10 weeks of gestation and then regress. The metanephric kidneys, which will develop over time into fully functional kidneys, begin to develop in the fifth week of gestation. By the tenth week of gestation, the primitive glomerulus has formed and is producing urine. The kidney continues to develop until a full complement of nephrons is present at 34 weeks of gestation or around a body weight of 2300 g. However, the glomerular and tubular functions continue to mature throughout the first years of life. The infant has a relatively low GFR (even when corrected for the smaller body surface area), which rapidly increases by 2 months of life and reaches adult values after 1.5 years of age (Table 29.4);

Table 29.4 Plasma CR-EDTA clearance in normal infants and children

Age (mo)	Mean GFR ± SD (ML/MIN/1.73 m^2)
<1.2	52.0 ± 9.0
1.2–3.6	61.7 ± 14.3
3.6–7.9	71.7 ± 13.9
7.9–12	82.6 ± 17.3
12–18	91.5 ± 17.8
18–24	94.5 ± 18.1
>24	104.4 ± 19.9

Revisiting normal (51)Cr-ethylenediaminetetraacetic acid clearance values in children. Adapted from: Piepsz (2006)

there is a similar maturation in the tubular function. The newborn kidney is able to function adequately to allow for growth and development but has limited ability to adapt in times of physiologic stress. For example, the immature acidification mechanisms can lead to acidemia during times of stress. In addition, the newborn kidney has limited ability to adjust the concentration of the urine, resulting in a tendency to water imbalances with subsequent disturbances in serum sodium. Newborns are susceptible to both hyponatremia due to water overload and hypernatremia due to water deficit. This can be compounded by the fact that newborn kidneys have higher sodium levels in the urine, with a higher obligate fractional excretion of sodium (FENa). In term infants, the FENa falls within the first few days of life, while sodium wasting persists for several days in preterm infants. Preterm infants often require sodium supplementation due to renal sodium wasting. Medications which further impair urinary concentration, such as diuretics, can lead to significant sodium wasting in infants even at relatively low doses.

29.3.2 Exogenous GFR Markers

The ideal substance to measure GFR would be in a steady state in the blood and urine, be freely filtered, not be removed except by excretion in the urine, and not be secreted or reabsorbed in the tubules.

There are a number of ways to determine GFR for an individual (Table 29.5). The ideal substance to measure GFR would be in a steady state in the blood and urine, be freely filtered, not be removed except by excretion in the urine, and not be secreted or reabsorbed in the tubules. Inulin is an example of such a substance and as such can be used to determine GFR. However, in routine clinical practice, GFR determination using inulin is not practical due to the fact that it is not readily available. In addition, it requires a prolonged infusion, coordination of blood and urine collection, and laboratory assays that are not routinely available. As a substitute, radiolabeled compounds such as iothalamate, diethylenetriaminepentaacetic acid (DTPA), and ethylenediaminetetraacetic acid (EDTA) can be infused, and the clearance can be calculated from a urine collection or from plasma disappearance. Disadvantages to standard radiotracer clearance methods include overestimation of GFR due to renal tubular secretion, patient and caregiver exposure to a radioactive substance, and difficulty in obtaining an accurate urine collection, particularly in children with urologic abnormalities. An alternate method, which does not depend on urine collection, involves giving a bolus injection of the radiotracer and measuring the plasma disappearance. The GFR can be estimated from the data points available by applying them to an established model for tracer elimination. Iohexol, a nonradioactive, nonionic, low-osmolar X-ray contrast medium (Omnipaque), can be substituted for radiotracers. It is excreted nearly exclusively in the urine with complete clearance within 24 h. Iohexol has demonstrated close agreement with estimates of GFR by inulin clearance and is an excellent agent to measure GFR by plasma disappearance. GFR can also be estimated by endogenous substances, which are eliminated primarily by the kidney with limited secretion or reabsorption, such as creatinine, urea, and cystatin C.

29.3.3 Creatinine Clearance

Given the difficulties with the most accurate methods for estimating GFR, methods which do not require specialized procedures and/or laboratory assays are often used to estimate GFR. Creatinine clearance is commonly used through collection of a 24-h urine, measurement of plasma creatinine, and

Table 29.5 Estimation of glomerular filtration rate (GFR)

Method	Limitations	Direction of error
Radiotracers (Iothalamate, DTPA, EDTA)	Radioactive	Iothalamate overestimates GFR
	Plasma disappearance preferred over urinary clearance	DTPA variable
	Iothalamate is secreted by the kidney EDTA not available in USA	
Iohexol	Plasma disappearance preferred over urinary clearance	None
Serum creatinine	Varies with age	Variable Ht/Scr is useful GFR estimator
	Only valid in steady state	
	May misrepresent GFR in multiple clinical situations:	
	Extremes of age and body size	
	Severe malnutrition or obesity	
	Diseases of skeletal muscle	
	Paraplegia or quadriplegia	
	Extremes of diet	
Creatinine clearance	Secreted by tubule	Overestimates GFR w/o cimetidine
	Varies with growth	
	Requires urine collection	
Urea clearance	Reabsorbed by the tubules	Underestimates GFR
	Sensitive to changes in volume status Requires urine collection	
Cystatin C	High-dose steroids Hyperthyroidism	Underestimates GFR, but useful GFR estimator

DTPA diethylenetriaminepentaacetic acid, *EDTA* ethylenediaminetetraacetic acid, *GFR* glomerular filtration rate, *Ht/Scr* height/serum creatinine concentration, *w/o* without

calculation of GFR. Creatinine is a breakdown product that is released as a result of metabolism of skeletal muscle. In states of good health, the concentration in the blood is relatively stable and a steady state exists. However, variation in creatinine production can occur in a number of different situations, including with meat consumption, exercise, and fever. This violates the steady-state assumption upon which the calculation of GFR is based, leading to inaccurate estimates of GFR. Creatinine is freely filtered into the urine but has some secretion in the tubule. With normal kidney function, creatinine clearance overestimates the true GFR by 10–20%. With decreasing GFR, there is an increase in creatinine secretion, increasing the magnitude of error. Thus, even when kidney function is significantly reduced, estimated GFR using creatinine

clearance may be normal. This effect can be minimized by the administration of cimetidine, an H_2 blocker that competitively inhibits creatinine secretion by the renal proximal tubule. An additional factor that limits the utility of creatinine clearance to estimate GFR is the difficulty in performing a timed urine collection in children.

29.3.4 Serum Creatinine

Normal values for creatinine must be correlated with age-appropriate reference ranges.

Serum creatinine is often utilized as a surrogate marker of renal function due to the ease of use. Serum creatinine is dependent on a number of different factors, including age, sex, muscle mass, and renal function. In newborns, there is an additional load of maternal creatinine. Normal values for creatinine must be correlated with age-appropriate reference ranges (Table 29.6). Within the first 24 h of life, the serum creatinine of the infant reflects maternal serum creatinine. Within a few hours of birth, the creatinine rises by approximately 0.1 mg/dL, probably secondary to a physiological decrease in extracellular volume. The serum creatinine subsequently gradually decreases, approximating 0.4 mg/dL by the second week of life. In preterm infants, it may take significantly longer for the serum creatinine to fall. Following the initial decline, serum creatinine is relatively stable for the first 2 years of life as GFR and muscle mass rise proportionally. After 2 years, creatinine gradually increases with age. Males have higher values than females due to increased muscle mass.

The methods used to measure creatinine also cause variability in results. The Jaffe reaction, first described in 1886, is a colorimetric assay in which the addition of an alkaline picrate solution results in a red compound that absorbs light at a constant wavelength. There are a number of compounds which can be present in the serum and which can produce either positive or negative interference, usually leading to an overestimation of creatinine. Examples of interfering substances include cephalosporins, ascorbic acid, glucose, bilirubin, and furosemide. In order to decrease the interference, there have been many modifications to the Jaffe method, particularly when performed by an autoanalyzer. However, the method still tends to produce an overestimation of creatinine. A more accurate method to measure creatinine is the enzymatic method, which tends to yield lower values. In this method, enzymatic cleavage of creatinine produces a colored product that tends to have less interference. A final method,

Table 29.6 Normal values, serum creatinine by age

Age	Creatinine (mg/dL)	Creatinine (mmol/L)
Cord	0.6–1.2	53–106
Newborn	0.3–1.0	27–88
Infant	0.2–0.4	18–35
Child	0.3–0.7	27–62
Adolescent	0.5–1.0	44–88
Adult, male	0.7–1.3	62–115
Adult, female	0.6–1.1	53–97

Adapted from The Harriet Lane Handbook 18th ed. Copyright © 2009

which has high specificity but is more time-consuming, is high-performance liquid chromatography (HPLC). As a result of the variability in the methods used to measure creatinine, it is important to utilize a laboratory which is calibrated to reference materials approved by the International Federation for Clinical Chemistry (IFCC); for example, creatinine testing should be calibrated to a traceable reference method (Isotope Dilution Mass Spectrophotometry or IDMS), resulting in more accurate and standardized creatinine results. In pediatric practice, however, age-specific normal values may not be available, resulting in the use of estimates from the literature.

In a steady state, with a stable serum creatinine and constant production of creatinine, serum creatinine and GFR will be inversely proportional.

$$\mathrm{GFR} \,\alpha\, 1/\mathrm{Cr}$$

Thus, a doubling of serum creatinine will reflect a 50% decrease in GFR. At lower values of creatinine, small changes may reflect a significant drop in GFR, while at a higher creatinine, a larger change in creatinine may represent only slight deterioration in renal function (Fig. 29.13). For example, a change in serum creatinine from 1 to 2 mg/dL may represent a drop in GFR from 120 to 60 mL/min. In contrast, creatinine increasing from 6 to 8 mg/dL can correlate with only a small decrease in GFR, such as from 20 to 15 mL/min. There have been numerous attempts to determine an accurate and clinically useful mathematical formula to estimate GFR from a steady-state creatinine. One of the most well known in adults is the Cockcroft-Gault equation:

$$\mathrm{Male}\,\mathrm{CL_{cr}}\left(\mathrm{mL/min}\right) = \frac{\left(140 - \mathrm{age\,in\,years}\right)\times\left(\mathrm{lean\,body\,weight\,in\,kg}\right)}{P_{\mathrm{cr}}\times 72}$$

$$\mathrm{CL_{cr}}\left(\mathrm{women}\right) = \mathrm{CL_{cr}}\left(\mathrm{men}\right)\times 0.85$$

where CL_{cr} is the creatinine clearance and P_{cr} is the serum creatinine value (mg/dL).

Creatinine clearance can also be estimated in the same manner as inulin clearance is used to approximate GFR (see above). Creatinine clearance over a given time interval (most often a 24-h urine collection) can be calculated using the following formula:

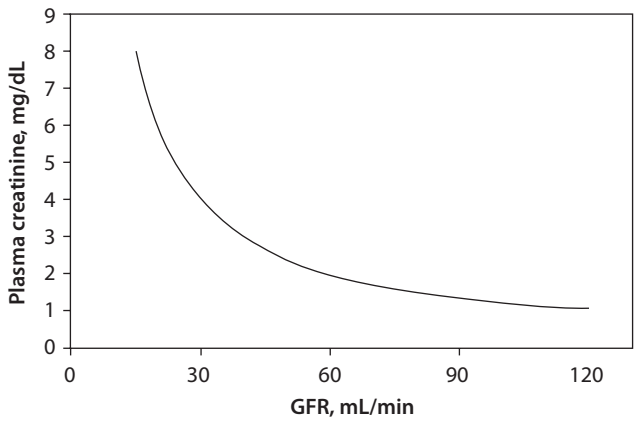


Fig. 29.13 Idealized steady-state relationship between plasma creatinine and GFR. Graph of an idealized relationship between the steady-state levels of serum creatinine and glomerular filtration rate (*GFR*) in adult patients. It is evident that even a mild increase in serum creatinine in patients with apparently normal kidney function may be associated with a marked decrease in GFR (the flat component of the curve toward the lower, right side of the curve)

$$\mathrm{CL_{cr}}\left(\mathrm{mL/min}\right)=\frac{U_{\mathrm{cr}}\times V_{\mathrm{u}}\left(\mathrm{mL/min}\right)}{P_{\mathrm{cr}}}$$

where V_u is the volume of urine produced per minute over the time interval. Using this equation, a 10 kg child with urine output of 3 mL/kg/hr. over a 24 h period would have a urine flow rate of 0.5 mL/minute. If the urine creatinine is 100 mg/dL and a plasma creatinine is 1 mg/dL, the child would have a CL_{Cr} = 50 mL/min as demonstrated:

$$\mathrm{CL_{Cr}}\left(\mathrm{mL/min}\right)=\frac{100\,\mathrm{mg/dL}\times 0.5\,\mathrm{mL/min}}{1\,\mathrm{mg/dL}}$$

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In a steady state, serum creatinine and GFR are inversely proportional. As a result, at lower values of creatinine, small changes may represent a significant deterioration in GFR.

The calculated clearance can then be corrected to the standard body surface area using the following formula:

$$\mathrm{Corrected\,CL_{Cr}}\left(\mathrm{mL/min/1.73\,m^2}\right)=\mathrm{CL_{Cr}}\left(\mathrm{mL/min}\right)\times 1.73/\mathrm{BSA}$$

Over 20 years ago, the Abbreviated Modification of Diet in Renal Disease (MDRD) Study equation was developed, and it has gained more widespread use:

$$\begin{aligned}\mathrm{GFR}\left(\mathrm{mL/min/1.73m^2}\right)=&\left(186\times\left(\mathrm{P_{cr}}\right)\right)-\left(1.154\times\mathrm{age}\left(\mathrm{years}\right)\right)-\\&\left(0.203\times 0.742\left(\mathrm{if\ female}\right)\right)\times\\&1.210\left(\mathrm{if\ African\ American}\right)\end{aligned}$$

The MDRD Study equation has been found to be more accurate and precise in individuals with a GFR less than 90 mL/min/1.73 m^2. It has been validated and has the advantage of not requiring weight or height.

More recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine equation developed from the urinary clearance of iothalamate in over 5000 adults has provided a good estimate of GFR in adults with CKD stages 1 to 4:

$$\begin{aligned}\mathrm{eGFR}\left(\mathrm{mL/min/1.73m^2}\right)=&141\times\min\left(S_{\mathrm{cr}}/k,1\right)^{\alpha}\times\max\left(S_{\mathrm{cr}}/k,1\right)^{-1.209}\times\\&0.993^{\mathrm{Age}}\times 1.018\left[\mathrm{if\ female}\right]\times 1.159\left[\mathrm{if\ black}\right]\end{aligned}$$

where: S_{cr} is serum creatinine in mg/dL,

- κ is 0.7 for females and 0.9 for males,
- α is −0.329 for females and − 0.411 for males,
- min indicates the minimum of S_{cr}/κ or 1, and
- max indicates the maximum of S_{cr}/κ or 1.

Unfortunately, neither Cockroft-Gault, MDRD, nor CKD-EPI equations can be used in the pediatric age group. In children and adolescents, GFR can be estimated from the serum creatinine (for use with creatinine methods with calibration traceable to isotope dilution mass spectrometry) using the bedside Schwartz equation:

$$\mathrm{eGFR}\left(\mathrm{mL/min/1.73\,m^2}\right)=\frac{0.41\times\mathrm{Height}\left(\mathrm{cm}\right)}{\mathrm{Creatinine}\left(\mathrm{mg/dL}\right)}$$

Using the bedside Schwartz equation, the GFR could be estimated for the child (75 cm height) in the above example as:

$$\mathrm{eGFR}\left(\mathrm{mL/min/1.73\,m^2}\right)=\frac{0.41\times 75\,\mathrm{cm}}{1\,\mathrm{mg/dL}}$$

The GFR estimates to 31 mL/min/1.73m^2. In the National Institutes of Health (NIH)-funded CKiD study, the parameter Height(cm)/S_{cr} (where S_{cr} is the serum creatinine concentration in mg/dL) correlated well with measured GFR in children with chronic kidney disease. Presumably, the height is proportional to muscle mass so that with growth and development children become taller such that their muscle mass increases, but this increases serum creatinine, a waste product of muscle metabolism. Therefore, the parameter Ht/S_{cr} reliably and accurately estimates GFR.

In clinical situations in which there is a rapid change in creatinine, such as in acute renal failure, there is a lack of steady state, and formulas used to estimate clearance from serum creatinine will not be valid.

There are a number of situations in which the equations for GFR may misrepresent the true kidney function. These situations include extremes of age and body size, severe malnutrition or obesity, diseases of skeletal muscle, paraplegia or quadriplegia, and extremes of diet. In addition, these equations were developed and intended to be used when there is a steady state in terms of creatinine production and clearance. However, in clinical situations, there is often a lack of steady state. In situations such as acute kidney injury, an abrupt fall in GFR results in increasing serum creatinine until a new steady state is reached. Similarly, with improvement in renal function, there will be a gradual reduction in creatinine. While serum creatinine is a useful marker of renal function in these cases, it must be recognized that quantitative evaluation of function cannot accurately be performed using these formulas which assume a steady state. However, in states of acute illness with fluctuating renal function, there are often few alternatives for estimating GFR for the purpose of adjusting drug doses. In these cases, it becomes critically important to closely monitor serum levels of drugs such as gentamicin and vancomycin, which are dependent on renal clearance. In addition, it is important to observe for signs of toxicity for drugs that are particularly sensitive to changes in GFR, such as acyclovir. Finally, it is important to constantly reevaluate the estimated clearance and to adjust drug doses based on the best estimate of GFR that is available.

In early renal disease, there can be as much as a 50% decrease in nephron mass without any detectable increase in serum creatinine.

Physiologically, there are inherent limitations to the use of creatinine as a marker of renal function. In early renal disease, there can be as much as a 50% decrease in nephron mass without any detectable increase in serum creatinine. This is due to compensatory hypertrophy of the remaining nephrons, intrinsic mechanisms that raise glomerular capillary pressure despite the destruction of the glomerular basement membrane and increased tubular secretion of creatinine. As a result, serum creatinine in pathological states may remain in the normal range until there is significant destruction of renal parenchyma. In summary, serum creatinine, while widely used and readily available, has many inherent flaws as a marker of renal function due to difficulties in measurement, a lack of a true steady state with constant variations in production and elimination, and difficulty in generating accurate estimations of true GFR.

29.3.5 Urea

Urea is a metabolic product that is formed when amino acids are metabolized in the liver but not used for protein synthesis. In order to prevent the accumulation of toxic levels of ammonium, NH_3 combines with CO_2 through the series of reactions of the urea cycle to form urea and water. Thus, urea production is augmented with high protein intake and/or with catabolic states such as critical illness, trauma, gastrointestinal bleeding, and corticosteroid administration. With severe malnutrition or liver disease, urea production is decreased. Urea is similar to creatinine in that it is removed primarily through excretion in the urine, and blood urea nitrogen (BUN) tends to vary inversely with GFR. It differs in that levels may vary widely between individuals because so many dif-

Since much of urea reabsorption is passively linked to sodium and water reabsorption, in any state where there is depletion of effective circulating volume, serum BUN will increase without any associated change in GFR.

ferent factors influence production. In addition, 45–50% of filtered urea is normally reabsorbed by the tubules due to a passive process linked with sodium and water reabsorption. Thus, in any state where there is effective circulating volume depletion, serum BUN will increase without any associated change in GFR. During states of hypovolemia, there is avid sodium and water retention, which results in passive reabsorption of urea. A decrease in GFR with reduced clearance of urea can also result in an elevated BUN. When BUN is noted to be elevated, it is useful in these situations to compare the ratio of BUN to creatinine (BUN:Cr). With a decreased GFR, both BUN and Cr should increase, while in hypovolemia with intact renal function, the BUN will rise disproportionately. A BUN:Cr ratio exceeding 20:1 is indicative of increased urea production or effective circulating volume depletion. With isolated renal disease, the BUN:Cr ratio will generally be less than 10 to 20:1.

A 24-h urine urea collection can also be used to estimate GFR, recognizing that it will underestimate the true GFR because of tubular reabsorption (Table 29.5). Since creatinine clearance overestimates GFR due to tubular secretion, an alternate method for estimating GFR is to calculate the clearance of both creatinine and urea and average them. In light of the inaccuracies in collecting urines, this computation is not commonly used in pediatric medicine.

$$\mathrm{GFR} = \left(\mathrm{CL_{cr}} + \mathrm{CL_{urea}}\right)/2$$

29.3.6 Cystatin C

Cystatin C is an endogenous and constantly produced 13 kDa protein that serves to inhibit cysteine proteases. It is freely filtered at the glomerulus, not secreted by the tubules, and is reabsorbed and catabolized with little urinary excretion. Unlike creatinine, cystatin C is not affected by muscle mass or much by race, age, or sex. On the other hand, cystatin C concentration is affected by large doses of corticosteroids, obesity, and thyroid disease. Cystatin C has now been standardized to an IFCC-approved reference material in the USA and Europe. The concentration of cystatin C is often well correlated with measured GFR in a variety of pediatric and adult populations, including the CKiD study. Indeed, subtle decrements in GFR are more readily detected by changes in serum cystatin C than creatinine, in part because of the shorter half-life of cystatin C.

CKiD has developed in children with chronic kidney disease and published a univariate cystatin C GFR estimating equation:

$$\mathrm{eGFR}\left(\mathrm{mL/min/1.73m^2}\right) = 81.84 \times \left(\mathrm{cysC}\right)^{-0.931}$$

where cysC is cystatin C concentration calibrated to IFCC-approved reference materials.

However, the best estimates of GFR in children and adults are obtained using a combination of serum creatinine and cystatin C. The combined formula from CKiD has been well correlated with measured GFR in children 1.5–18 years of age and again is best utilized when the patient is in a steady state:

$$\begin{aligned}\mathrm{eGFR}\left(\mathrm{mL/min/1.73m^2}\right) = {} & 39.8 \times \left[\mathrm{Ht}/S_{\mathrm{cr}}\right]^{0.456} \times \left[2.11/\mathrm{cysC}\right]^{0.418} \\ & \times \left[30/\mathrm{BUN}\right]^{0.079} \times \left[1.076^{\mathrm{male}}\right]\left[1.00^{\mathrm{female}}\right] \\ & \times \left[\mathrm{Ht}/1.4\right]^{0.179}\end{aligned}$$

where Ht is height in meters, S_{cr} is standardized serum creatinine in mg/dL, cysC is cystatin C calibrated to IFCC-approved reference materials, and BUN is blood urea nitrogen concentration.

After age 18, when the CKD-EPI equation is routinely applied to estimate kidney function in adolescents, there is a sharp overestimation of measured GFR. One method to estimate GFR in adolescents above 18 and under 26 is to take the average of CKD-EPI creatinine-based eGFR and the Schwartz bedside creatinine-based eGFR:

$$\text{eGFR of adolescent}\left(\text{mL}/\text{min}/1.73\text{m}^2\right) = \left[\begin{pmatrix}\text{CKD EPI} + \\ \text{Schwartz}\,0.413 \times \left(\text{Ht}/S_{cr}\right)\end{pmatrix}\right]/2.$$

There is a need to develop equations to estimate GFR in infants. The previous Schwartz estimates are not valid using current enzymatic IFCC-approved reference materials. However, we have found that by using and preserving the ratio of 0.413/0.55 = 0.75 and multiplying this by the previous estimates (0.45 for term and 0.33 for preterm), the following equations work fairly well for estimating GFR in infants:

$$\text{Term baby eGFR} = 0.75 \times 0.45 \times \text{Ht}\left(\text{cm}\right)/S_{cr}\left(\text{mg}/\text{dL}\right)$$

$$\text{Term baby eGFR} = 0.32 \times \text{Ht}\left(\text{cm}\right)/S_{cr}\left(\text{mg}/\text{dL}\right)$$

$$\text{Preterm baby eGFR} = 0.75 \times 0.33 \times \text{Ht}\left(\text{cm}\right)/S_{cr}\left(\text{mg}/\text{dL}\right)$$

$$\text{Preterm baby eGFR} = 0.25 \times \text{Ht}\left(\text{cm}\right)/S_{cr}\left(\text{mg}/\text{dL}\right)$$

It is important to note that these infant eGFRs have not yet been formally validated by direct measurement of GFR.

29.4 Water and Salt Balance: Overview

Adequate renal function is necessary for clearance of metabolic products. Adjustment of the amount and composition of urine is critical for the maintenance of adequate effective circulating volume and a stable extracellular milieu. The kidney responds to a number of different hormones to regulate salt and water balance (Table 29.7). Water balance is regulated by maintaining the plasma osmolality within a narrow range, normally 275–290 mOsm/kg.

The *ratio* of sodium to water, the serum sodium concentration, is reflective of the water balance, while volume status is determined by the total body *quantity* of sodium and water.

Table 29.7 Regulation of serum osmolality and effective circulating volume

Factor regulated	Clinical correlate	Main regulatory factors	Net effects
Serum osmolality	Sodium concentration	ADH, thirst	Water intake, urine concentration/dilution
Effective circulating volume	Total body sodium, blood pressure, perfusion	Renin-angiotensin II-aldosterone axis, ANP, sympathetic nervous system	Salt and water retention

Adapted from Rose and Post (2001)
ADH antidiuretic hormone, *ANP* atrial natriuretic peptide

Osmolality is determined by the number of particles which are present within a given compartment. The unit of measurement for osmolality is the osmole. One osmole contains 6.02×10^{23} particles and is equal to 1 mole of a non-dissociable substance. Within the body, in order to be an effective osmole, the solute cannot freely cross membranes. Substances such as urea which freely diffuse across cell membranes cannot generate an osmotic pressure gradient and are ineffective osmoles. The main intracellular osmoles are potassium salts, while the extracellular fluid contains mainly sodium salts as effective osmoles. Thus, the serum sodium *concentration* is usually reflective of the amount of water relative to the amount of solute. When there is too little water relative to solute, hypernatremia is indicative of the imbalance of the ratio of solute to water. In contrast, too much water relative to sodium leads to dilution and hyponatremia. Regulation of water balance, and hence serum osmolality, is primarily through water intake (thirst) and ADH secretion. ADH production results in the formation of a concentrated urine, with net retention of water. Although the ratio of sodium compared to water is important, the total body *quantity* of sodium is also important. As the major extracellular solute, total body sodium is usually reflective of the amount of fluid in the extracellular fluid compartment. Regulation of volume status is a more complicated process which involves multiple feedback loops, including the renin-angiotensin II-aldosterone axis, atrial natriuretic peptide (ANP), and the sympathetic nervous system. In summary, water balance is reflected by the concentration of sodium (the ratio of solute to water), while volume status is determined by the total quantities of sodium and water which are present.

29.4.1 Maintenance of Effective Circulating Volume

In order to prevent tissue hypoxia, there must be an adequate volume of blood, and it must be perfusing the tissues effectively such that oxygen is delivered.

Adequate oxygen delivery to the body is vital during critical illness. Oxygen is carried by the blood within the circulatory system. To prevent tissue hypoxia, there must be adequate blood within the circulation, and it must be effective in reaching the tissues. This concept is known as effective circulating volume (ECV), reflecting the fact that not only must there be an adequate volume of blood, but it must be perfusing the tissues effectively to ensure oxygen delivery. The distinction between total intravascular volume and effective circulating volume can be important in pathological states. For example, in chronic heart failure, there is adequate volume, but due to poor cardiac output, it is not circulating effectively and low blood pressure is sensed by baroreceptors. This leads to renal retention of salt and water in an attempt to improve perfusion, resulting in edema and total body fluid overload.

The regulation of effective circulating volume is a complicated process involving multiple hormones. The sequence of events in response to decreased effective circulating volume includes immediate responses by the sympathetic nervous system to maintain systemic blood pressure, followed by a regulatory response which results in salt and water retention by the kidneys in an attempt to increase the intravascular volume. Decreased perfusion is sensed by activation of pressure or stretch receptors in the cardiopulmonary circulation, the carotid sinuses, and the aortic arch. This results primarily in increased sympathetic nervous system activity, although with more severe dehydration, ADH is also released. Changes in atrial stretch receptors lead to the release or suppression of natriuretic peptides. For example, in hypovolemia, there is a reduction in the release of the sodium-losing hormone ANP. In contrast, in congestive heart failure, there are increased atrial pressures leading to markedly elevated levels of ANP. Within the kidney, baroreceptors in the afferent glomerular

arterioles react to impaired renal perfusion pressure in various disease states, leading to renin release. The macula densa also releases renin in response to a low distal delivery of sodium chloride.

29.4.2 Effects of Renin/Angiotensin II

Renin is a proteolytic enzyme which is manufactured and released by the kidney. Prorenin is synthesized by the juxtaglomerular cells located in the afferent arteriole of the glomerulus. Prorenin is then cleaved to renin, which is stored in secretory granules. In states of low perfusion pressure, renin is released in response to activation of the sympathetic nervous system, decreased sodium and chloride delivery to the cells of the macula densa, or decreased pressure sensed by the baroreceptors of the afferent arteriole (Fig. 29.11). Acute changes result in renin release from preformed secretory granules, while chronic stimulation causes increased synthesis of prorenin and renin. Renin then catalyzes the cleavage of angiotensinogen into the decapeptide angiotensin I. Angiotensin converting enzyme (ACE), produced in the lung, kidney, and elsewhere, converts angiotensin I into the octapeptide angiotensin II (AII). The main actions of renin are due to AII, which has a number of effects including mediating vasoconstriction and increased blood pressure and also increasing secretion of aldosterone from the adrenal cortex, which increases sodium reabsorption in the cortical collecting duct and leads in the same segment to secretion of H^+ and K^+.

Two important effects of renin release are AII-mediated aldosterone release and systemic and renal vasoconstriction.

Within the kidney, AII causes arteriolar vasoconstriction, efferent more than afferent, leading to increased glomerular capillary pressure which helps to elevate glomerular hydraulic pressure to maintain GFR when the system is activated by a fall in systemic pressure via autoregulation. However, in order to prevent compromise of renal blood flow by excessive vasoconstriction of the renal vessels, AII causes prostaglandin release within the glomerulus, leading to protective vasodilation. This relates to the mechanism by which nonsteroidal anti-inflammatory agents (NSAIDS) increase the kidney's susceptibility to ischemia in the face of hypovolemia. Blockade of prostaglandin release can lead to unopposed vasoconstriction. Other actions of AII include a direct effect on the cells of the proximal tubule to stimulate sodium reabsorption, constriction of the glomerular mesangium to reduce surface area available for filtration, and increased sensitivity to tubuloglomerular feedback. The net effect on GFR is variable, depending on the ambient levels of AII. AII can also act as an inflammatory mediator and promote cellular proliferation leading ultimately to fibrosis.

29.4.3 Aldosterone

Aldosterone is a mineralocorticoid which is synthesized in the zona glomerulosa of the adrenal gland. Aldosterone is secreted in response to activation of the renin/angiotensin system with subsequent production of angiotensin II, which stimulates aldosterone production. Hyperkalemia also has a direct effect on the aldosterone-producing cells, with a synergistic effect occurring if both hyperkalemia and AII are present. Other factors which are not primary regulators, but which can enhance aldosterone production, include adrenocorticotropic hormone (ACTH) and hyponatremia. In contrast, ANP and hypernatremia can suppress aldosterone production. In the pathological state of glucocorticoid remedial hypertension, a chimeric gene results in the produc-

Aldosterone stimulates the secretion of K^+ and H^+ and the reabsorption of Na^+ and Cl^-, with an increase in blood volume as water accompanies the sodium and chloride.

tion of aldosterone synthase in the zona fasciculata, making aldosterone synthesis dependent on ACTH. In this condition, if ACTH is suppressed by the administration of physiological levels of exogenous corticosteroids, the hypertension resolves.

The effect of aldosterone on the distal nephron (connecting segment and cortical collecting duct) is to stimulate reabsorption of Na^+ and Cl^- and secretion of K^+ and H^+, with an increase in blood volume as water accompanies the sodium and chloride. Aldosterone acts by binding to mineralocorticoid receptors. Aldosterone and cortisol both bind to aldosterone receptors with equal affinity. However, under normal circumstances, there are enzymes, such as 11-β-hydroxysteroid dehydrogenase, which are present in target tissues and convert cortisol to cortisone, which is not able to bind/activate the mineralocorticoid receptor. Licorice and some chewing tobaccos contain glycyrrhetinic acid, an inhibitor of this inactivating enzyme. As such, excessive intake of licorice leads to cortisol activation of aldosterone receptors, resulting in apparent primary mineralocorticoid excess with a clinical picture of hypertension, hypokalemia, and metabolic alkalosis.

The most important site of action of aldosterone is the principal cells of the cortical collecting tubule. Aldosterone diffuses into the cell and binds to a cytosolic receptor, which opens Na^+ and K^+ channels on the luminal membrane and stimulates Na^+-K^+ATPase on the basolateral membrane (Fig. 29.14). As a result of this action, three Na^+ molecules leave the cell to return to the systemic circulation, and two K^+ molecules enter the cell, creating a low concentration of sodium in the cell and an electronegative interior. These gradients favor the diffusion of sodium through the open luminal sodium channels (amiloride-sensitive sodium channels). The movement of sodium out of the lumen results in a lumen-negative potential, which either drives the passive reabsorption of chloride paracellularly or the secretion of potassium through the aldosterone-sensitive potassium channels in the luminal membrane. This system is so efficient at sodium removal that the urinary sodium content can be lowered to less than 5 mEq/L in the presence of hypovolemia. Liddle syndrome occurs when a mutation of the amiloride-sensitive epithelial sodium channel (ENaC) results in the channel remaining constitutively open. This leads to a clinical state similar to hyperaldosteronism with hypertension, sodium retention, and potassium wasting. The opposite condition, pseudohy-

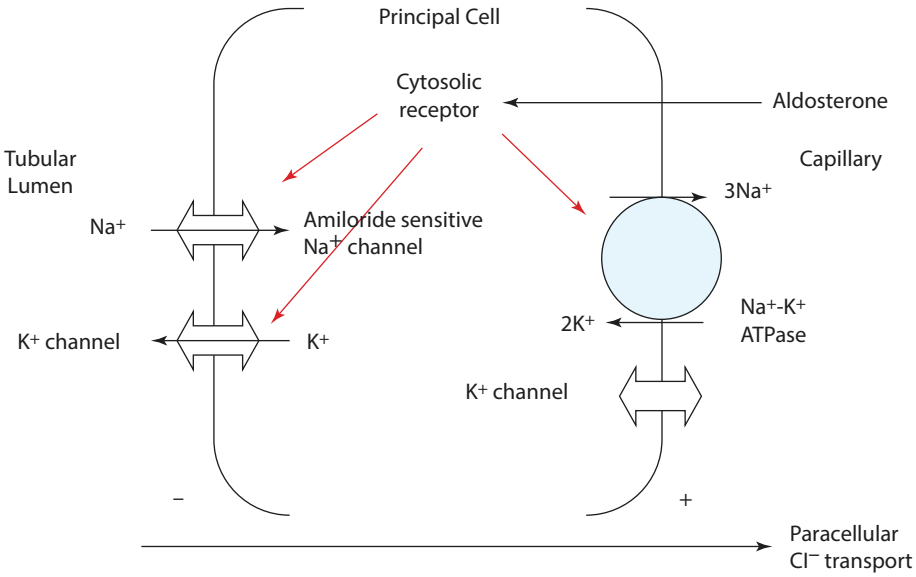


Fig. 29.14 Diagram depicting the effects of aldosterone on Na^+ and K^+ transport by the principal cell of the cortical collecting duct. Luminal Na^+ enters through an apical channel (ENaC), and the negative transepithelial voltage caused by this movement facilitates the secretion of K^+ or the paracellular reabsorption of Cl^-. Aldosterone is a key factor in these transport processes and acts through a cytosolic receptor to primarily increase the number of open Na^+ channels in the apical membrane. There are also secondary effects to increase the activity of Na^+-K^+ ATPase and the number of open K^+ channels

poaldosteronism, occurs with an inactivating mutation of ENaC in which there is the appearance of a hypoaldosterone state with sodium wasting and hyperkalemia.

Aldosterone also stimulates proton secretion in the intercalated cells of the cortical and outer medullary collecting ducts by directly activating H^+-ATPase. There is also indirect stimulation of proton secretion due to the lumen-negative potential generated by sodium reabsorption. This will be discussed in more detail in the acid-base section.

29.4.4 Renal Sodium Handling

The kidney has a remarkable ability to adjust the urinary sodium and is able to produce a urine with a sodium concentration which ranges from 1 to 100 mEq/L. Although systemic effects of the sympathetic nervous system and AII release can raise blood pressure and improve perfusion temporarily, renal sodium retention is necessary to increase circulating volume and bring about a sustained response. Overall, the control of volume status, through regulation of urinary sodium handling, is a complicated process with multiple regulatory pathways. These multiple regulatory pathways provide redundancy of function, assuring that even if there is malfunction in one or more pathway, regulation of volume status is maintained.

It is clear that aldosterone plays a critical role in the day-to-day regulation of urinary sodium. However, there is evidence that other natriuretic factors, such as ANP, may play a role under conditions of increased sodium intake. Peptides, such as urodilatin and brain natriuretic peptide, may also play a role in inducing sodium excretion.

The main site of minute-to-minute regulation of urinary sodium is the collecting tubule. Although only 5% of filtered sodium is reabsorbed in the collecting tubule, the actions of aldosterone and ANP lead to constant readjustment of the final urine sodium concentration in response to changes in effective circulating volume. In contrast, the loop of Henle and the distal tubule have flow-dependent sodium reabsorption and hence are not normally sites of regulation. The proximal tubule has many factors which can affect sodium reabsorption, including AII, norepinephrine, and Na^+-H^+ exchange. This can become important in hypovolemic states, in which increased sodium reabsorption is accompanied by increased reabsorption of bicarbonate, urea, calcium, and uric acid. As a result, volume contraction can lead to a secondary hyperuricemia and metabolic alkalosis.

Although aldosterone and ANP are major regulatory pathways involved in regulation of volume status, there are many other ways in which the urinary sodium can be adjusted. An example of this is aldosterone escape. In the face of hyperaldosteronism, such as with an aldosterone-secreting tumor, after a few days of volume retention, there is a spontaneous diuresis. This is due to reduction of the urinary sodium reabsorption at aldosterone-independent sites, which may be mediated in part by ANP or may occur directly in response to increased renal perfusion pressure via pressure natriuresis. The mechanism of pressure natriuresis is not completely understood, but it occurs when small changes in the systemic blood pressure result in a significant decrease in sodium and water reabsorption in the proximal tubule and loop of Henle.

29.4.4.1 Atrial Natriuretic Peptide (ANP)

Atrial natriuretic peptide (ANP) is a 28-amino acid polypeptide which is released from cells within the atria in response to stretch. Carotid and renal baroreceptors may also affect release, and in states of chronic hypervolemia, the ventricular myocardium can also contribute to production. The physiologic role of ANP has not been established, but there are many actions of ANP with significant effect. The two primary actions of ANP are direct vasodilation and increased sodium and water excretion. It has multiple effects on the kidney which lead to natriuresis, including inhibition of medullary collecting duct sodium reabsorption, a direct increase in GFR, lower basal renin release, and inhibition of aldosterone secretion which in turn decreases the action of ADH in the collecting duct and inhibits the AII-mediated increase in sodium reabsorption in the proximal tubule.

29.4.5 Water Balance

Regulation of serum osmolality is accomplished by adjustment of water intake, via the thirst mechanism, and by ADH-mediated adjustment of urine concentration.

Water balance is controlled by the tight regulation of serum osmolality. The regulation of serum osmolality is accomplished by adjustment of water intake via the thirst mechanism and by ADH-mediated adjustment of urine concentration. Under normal circumstances, if there is an increase in serum osmolality, thirst will be stimulated. In addition, ADH will be released, leading to renal reabsorption of water in excess of sodium, resulting in concentrated urine. Both of these actions increase the amount of water present relative to solute, returning the serum osmolality to normal. The main factor which regulates body water content is the production of ADH. ADH, also known as vasopressin in humans, exists as arginine vasopressin. The synthetic form of ADH is 1-deamino-8-D-arginine vasopressin (DDAVP) known as desmopressin. ADH is secreted by the posterior lobe of the pituitary and has a half-life of only 15–20 min. ADH secretion in response to as little as a 1% change in serum osmolality has been demonstrated. By adjustments of water intake and ADH secretion, serum osmolality is maintained between 275 and 290 mOsm/kg. Below 275 mOsm/kg, ADH secretion is almost completely suppressed, while above 290 mOsm/kg, ADH secretion increases in a linear fashion in proportion to the plasma osmolality. Although serum osmolality is the main determinant of ADH secretion, ADH can be released in states of dramatically decreased effective circulating volume. ADH is not secreted until there is more than a 5–8% decrease in blood volume. Thus, it is only at the point at which hypotension would be evident clinically that ADH secretion is activated, resulting in dramatic increase in water retention. Other factors which can affect ADH secretion include drugs, nausea, surgery, pain, pregnancy, hypoglycemia, hypoxemia, and hypercarbia. The acute ADH release in response to hypoxemia and hypercarbia is additive when both stimuli are present and plays a role in the fluid retention accompanying respiratory insufficiency or failure.

ADH acts through two different receptors, V_1 receptors and V_2 receptors. Stimulation of V_1 receptors results in vasoconstriction and prostaglandin release. Prostaglandins block ADH actions and act as negative feedback. V_2 receptors mediate the antidiuretic response and are found primarily on the principal cells of the collecting ducts. Activation of V_2 receptors causes preformed cytoplasmic vesicles which contain water channels to fuse with the luminal membrane, a process known as receptor-mediated exocytosis. Aquaporin-2 is the principal ADH-sensitive water channel. Since the basolateral membrane is freely permeable to water and the interstitium is hypertonic, water then travels along the osmotic gradient out of the lumen, across the principal

cell, and into the interstitium to be reabsorbed. In order for this to be an effective system, the countercurrent multiplication system must be intact to create a high osmolality interstitium. The net effect is reabsorption of water with the subsequent decrease in plasma osmolality and production of concentrated urine with high osmolality. In the absence of ADH, the water channels are removed through endocytosis, and the urine is maximally dilute. In the absence of water channels, urine osmolality will be lower than 100 mOsm/kg and can be as low as 30–50 mOsm/kg. In the presence of maximal ADH, a urine concentration as high as 1000–1200 mOsm/kg can be reached.

Another ADH effect mediated through the V_2 receptors is the release of clotting factors VIII and von Willebrand factor (VWF) from the vascular endothelium. In healthy individuals, the physiological significance of this is not known, but this effect can be used therapeutically in the treatment of some bleeding disorders. For example, uremic patients may have platelet dysfunction and an increased bleeding time which may be markedly improved by the administration of DDAVP.

The syndrome of inappropriate ADH secretion (SIADH) and/or a decreased effective circulating volume may result in high levels of ADH that are not in response to increased serum osmolality. In both situations, laboratory evaluation will demonstrate evidence of ADH production leading to production of urine which is not maximally dilute despite a low serum osmolality. In states of decreased extracellular volume, such as hypovolemic shock, ADH is secreted appropriately in an attempt to increase total blood volume. Additional states which commonly involve relatively low effective circulating volume are hepatic cirrhosis and peripheral vasodilation. In the case of SIADH, ADH secretion occurs independently of serum osmolality and intravascular volume status. The retention of water leads to activation of volume receptors, leading to sodium excretion in the urine with the net result of hyponatremia without substantial edema. There are many causes of pathological ADH secretion including intracranial processes (such as hemorrhage or infection), medications, and pulmonary disease. It is important to note that water intake is necessary for the development of hyponatremia in SIADH. With water restriction, water retention and sodium excretion resolve and serum sodium normalizes.

In SIADH, ADH secretion occurs independently of serum osmolality and intravascular volume status. In states of decreased extracellular volume, ADH is secreted appropriately in an attempt to maintain adequate perfusion by increasing blood volume. In either case, laboratory evaluation will demonstrate evidence of ADH production with urine that is not maximally dilute despite a low serum osmolality.

Thirst, in addition to ADH, is an important regulator of serum osmolality. The thirst mechanism is so strong that even in situations of inadequate urinary concentration, such as diabetes insipidus, a normal or near normal serum sodium is often maintained. Laboratory abnormalities may not be observed unless the individual is denied access to water, such as in a water deprivation trial or in the cases of infants or those with severe psychomotor impairment who cannot effectively communicate their thirst.

29.4.6 Role of Renal Prostaglandins

Prostaglandins are derived from the metabolism of arachidonic acid, which is catalyzed by cyclooxygenase and other enzymes. Prostaglandins produced in the kidney have many local effects but little systemic activity due to rapid metabolism in the lung. The prostaglandins which have the most dominant action within the kidney are prostaglandin E_2 and prostacyclin. Within the kidney, they cause vasodilation which protects renal blood flow and GFR in the face of vasoconstriction. In states of euvolemia, their role is not critical; however, when hypovolemia is present, the effect of prostaglandins can be significant. A normal response to hypovolemia is release of renin leading to

In high renin states, such as hypovolemia, blocking prostaglandin actions with NSAIDs may result in renal ischemia due to unopposed renal vasoconstriction.

increased AII production. One effect of AII is systemic vasoconstriction with subsequent increase in blood pressure. The effect on the renal vasculature, however, is limited by renal prostaglandin production, allowing for maintenance of renal blood flow during these high renin states. If prostaglandin actions are blocked in high renin states, such as by the administration of nonsteroidal anti-inflammatory agents (NSAIDs), renal blood flow can be compromised by local vasoconstriction, leading to renal ischemia. Another effect of prostaglandins is to mediate an increase of renin secretion. Individuals with renal insufficiency can be very sensitive to the inhibition of this prostaglandin effect, with hyperkalemia resulting from lower levels of renin with decreased aldosterone production and subsequent reduction in urinary potassium excretion. A third effect of prostaglandins is to mitigate the effects of ADH, preventing excessive ADH secretion. Thus, hyponatremia can occur in patients taking NSAIDs. A final action of prostaglandins is to decrease sodium reabsorption in the thick ascending limb and collecting tubules. The decreased sodium absorption in the low oxygen medulla may help to keep the energy requirement low. Administration of NSAIDs promotes sodium reabsorption and can limit the efficacy of diuretics. Additionally, there is concern that NSAIDs may increase the likelihood of renal ischemic injury by preventing the prostaglandin-induced decrease in sodium absorption, particularly in states of hypovolemia, when the hypoxia is more severe.

29.5 Potassium Regulation

The three main factors that affect potassium secretion are aldosterone, the distal flow of sodium and water, and the serum potassium concentration.

Potassium is the major intracellular cation, with levels of about 140 mEq/L within the cell, while the serum level is maintained at about 4.5 mEq/L. Because potassium is a critical electrolyte in determining cell metabolism and the resting potential of the cell membrane, potassium levels are maintained within a narrow range. In response to a potassium load, there are mechanisms in place to shift some of the potassium into the cells in order to prevent an excessive rise in serum potassium. However, it is the kidney that is primarily responsible for the regulation of potassium through adjustment of the amount excreted in the urine. The filtered load of potassium is recovered through passive reabsorption in the proximal tubule and secondary active transport via the Na^+-K^+-$2Cl^-$ carrier in the loop of Henle. The regulation of potassium excretion in the urine is primarily determined by the principal cells in the cortical collecting tubule. There are three main factors which affect the potassium secretion: aldosterone, the distal flow of sodium and water, and the serum potassium concentration. Aldosterone, as previously mentioned, has many actions which promote the secretion of potassium. Aldosterone opens Na^+ and K^+ channels on the luminal membrane of principal cells and activates Na^+-K^+ATPase on the basolateral membrane, all of which promote movement of potassium into the lumen (Fig. 29.14). Reabsorption of sodium creates a lumen-negative potential which promotes the secretion of potassium through the aldosterone-sensitive potassium channels in the luminal membrane. If there is inadequate distal sodium delivery, decreased sodium reabsorption results in impaired potassium secretion due to a lack of lumen-negative potential to act as a driving force. Potassium secretion is also diminished when there is low distal flow of fluid. Normally, due to reabsorption of the filtered potassium proximally, the concentration in the collecting tubule is low. This favors movement of potassium out of the principal cells down a concentration gradient. In situations of low flow, this concentration gradient is diminished, and potassium secretion may be impaired. The opposite can also occur, with potassium wasting occurring

due to increased concentration gradient which occurs with increased distal flow rate, such as with diuretics. Although the collecting tubule is primarily responsible for potassium secretion, the intercalated cells are capable of potassium reabsorption due in large part to H^+-K^+ATPase in the luminal membrane, since the pump activity is increased with hypokalemia and inhibited with hyperkalemia.

29.6 Diuretics

Most diuretics disrupt sodium reabsorption, leading to the excretion of sodium and water.

Diuretics have a number of clinical applications, including the treatment of volume overload, edema, and hypertension. Diuretics can be classified according to their mechanism of action (Table 29.8). Most diuretics disrupt sodium reabsorption, leading to the excretion of sodium and water. Sodium reabsorption is powered by the Na^+-K^+ ATPase on the basolateral membrane. Pumping of sodium out of the cells keeps the intracellular concentration low, allowing for sodium from the ultrafiltrate to enter the cell down a favorable concentration gradient through a variety of channels or transporters on the luminal membrane. Many of the diuretics work by inhibiting entry of sodium into the cell. The three main classes of diuretics are loop diuretics, thiazides, and potassium-sparing agents. Loop diuretics work within the thick ascending limb of the loop of Henle. They compete for the chloride site on the Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle (Fig. 29.6). Although increased distal sodium reabsorption can compensate for some sodium lost due to loop diuretics, the net loss is still up to 25% of filtered sodium. Calcium reabsorption in this segment is passive and is driven by the lumen positivity created by NaCl reabsorption with potassium recycling. Loop diuretics block this process, leading to increased calcium excretion. This calciuric response can lead to kidney stones and nephrocalcinosis, especially in premature infants in whom a loop diuretic can cause more than a tenfold increase in calcium excretion.

Thiazide diuretics, which act on the distal convoluted tubule and connecting segment, are less potent, causing up to 3–5% of filtered sodium to be excreted. They cause sodium and water losses by blocking chloride transport through the electroneutral sodium chloride cotransporter. Both loop and thiazide diuretics cause loss of potassium in the urine due to increased aldosterone from volume depletion and as a result of increased distal sodium delivery and increased distal flow rate. Thiazides increase the reabsorption of calcium, reducing urinary calcium excretion. They are commonly used in the treatment of recurrent kidney stones due to hypercalciuria.

If a single diuretic is not having the desired effect, adding an agent which works at a different site within the nephron can increase potency.

The final class of diuretics is potassium-sparing diuretics. These agents work by acting on the principal cells in the cortical collecting tubule. Spironolactone works as an aldosterone receptor antagonist, while amiloride and triamterene directly inhibit the sodium channels in the luminal membrane. Potassium and proton excretions in this segment are both dependent on the electronegative potential which is generated by sodium reabsorption. When the sodium reabsorption is blocked, this also limits potassium and acid secretion, which can cause hyperkalemia and metabolic acidosis. The efficacy of this class is limited to 1–2% excretion of filtered sodium. Their potency can be increased significantly by combining them with an agent that works more proximally.

There are two additional types of diuretics which work by alternate mechanisms in the proximal tubule: osmotic agents and carbonic anhydrase inhibitors. Osmotic agents, such as mannitol, inhibit proximal sodium reabsorption through osmotic drag. They also increase blood flow to the medulla, decreas-

Table 29.8 Characteristics of diuretics

	Site of action	Specific agents	Special indications	Administration	Mechanism	Side effects
Carbonic anhydrase inhibitor	Proximal tubule	Acetazolamide (Diamox®)	Glaucoma Mountain sickness Urinary alkalinization	Oral/IV	Inhibits carbonic anhydrase	Metabolic acidosis Hypokalemia Nephrolithiasis
Osmotic	Proximal tubule Thin ascending limb of Henle	Mannitol	Increased intracranial pressure	IV	Osmotic inhibition of NaCl reabsorption Increased medullary blood flow	Plasma volume expansion Hyponatremia Hypokalemia
Loop diuretics	Thick ascending limb of Henle	Furosemide (Lasix®)	Hypercalcemia Hypermagnesemia Congestive heart failure	Oral/IV	Inhibition of Na^+-K^+-$2CL^-$ cotransporter	Hypokalemia Hyponatremia Hypocalcemia Hypomagnesemia Metabolic alkalosis Ototoxicity Allergic reaction
		Bumetanide (Bumex®)		Oral/IV		
		Ethacrynic acid		Oral/IV		
Thiazide	Distal convoluted tubule	Chlorothiazide (Diuril®)	Hypercalciuria Diabetes insipidus	Oral/IV	Inhibition of electroneutral NaCl channel	Hyponatremia Hypokalemia Impaired glucose tolerance Zinc deficiency Lipid abnormalities Allergic reaction
		Hydrochlorothiazide		Oral		
Thiazide-like	Distal convoluted tubule	Chlorthalidone		Oral	Inhibition of electroneutral NaCl channel	
		Metolazone (Zaroxolyn®)	Low glomerular filtration rate	Oral		
Potassium-sparing	Cortical collecting tubule	Spironolactone (Aldactone®)	Hypokalemia	Oral	Aldosterone receptor antagonist	Hyperkalemia Metabolic acidosis Gynecomastia Impotence
		Amiloride	Hypercalciuria Hypokalemia	Oral	Inhibition of sodium channel	Hyperkalemia Metabolic acidosis
		Triamterene	Hypokalemia	Oral	Inhibition of sodium channel	Hyperkalemia Metabolic acidosis Nephrolithiasis Pancytopenia

ing the medullary tonicity and impairing the countercurrent concentrating mechanisms, further reducing sodium reabsorption in the loop of Henle. Carbonic anhydrase inhibitors such as acetazolamide block the actions of carbonic anhydrase. This limits the reabsorption of filtered bicarbonate, causing bicarbonate wasting with consequent impaired sodium reabsorption. Side effects of carbonic anhydrase inhibitors include acidosis, hypokalemia, and nephrolithiasis. Both osmotic agents and carbonic anhydrase inhibitors have limited efficacy as diuretics if used alone since distal portions of the nephron experience increased sodium delivery and are able to compensate by increasing reabsorption. However, if a proximal agent is used in conjunction with an agent that blocks distal sodium reabsorption, the efficacy of these agents is dramatically increased.

29.7 Energy Requirement of the Normal Kidney

Most of the energy requirement of the kidneys is provided by ATP which is derived from oxidative metabolism and is used largely in the recovery of filtered sodium.

The kidney is a metabolically active organ, receiving 20% of cardiac output and accounting for about 10% of resting energy consumption. It is second only to the heart in oxygen consumption by weight. Most of the energy requirement of the kidneys can be attributed to the need for active solute transport in the recovery of filtered sodium. This is demonstrated by the linear correlation between sodium reabsorption and oxygen consumption in the kidney. The major source of energy is through generation of ATP, derived from oxidative metabolism. There are numerous substrates available to fuel oxidative metabolism, including lactate, glutamine, glucose, free fatty acids, citrate, and ketone bodies. The kidneys are energy efficient, using passive mechanisms such as paracellular diffusion and solute drag for a significant proportion of proximal sodium reabsorption. With adequate oxygen delivery, the kidneys have a large reservoir to increase metabolic activity if needed. This increases with age, and in adults under normal conditions, the proximal tubule functions at only 50–60% of maximal respiratory capacity.

In order for oxidative metabolism to continue without disruption, there must be adequate oxygen delivery to match consumption. The kidneys are dependent on renal blood flow to supply oxygen. The response of the kidney to decreased oxygen delivery is atypical in that the initial response to a decrease in renal plasma flow (RPF) is a decrease in oxygen demand and consumption. This occurs because decreased RPF, such as occurs due to hypotension or hypovolemia, leads to decreased GFR. The decreased GFR reduces the filtered sodium load, decreasing the amount of sodium to be reabsorbed and thereby limiting the energy requirement for active sodium transport. With falling RPF, GFR will fall to zero, leaving only the basal energy requirements of the kidney, about 100 μmol of oxygen per minute per 100 g of kidney. At this point, oxygen extraction is increased to meet metabolic needs. If renal blood flow continues to fall, and oxygen extraction is maximal, the basal energy requirements cannot be met and the cells begin to die, resulting in ischemic cell death.

Low oxygen delivery causes renal damage through multiple mechanisms. Impaired oxygen delivery leads to inadequate ATP production, impairing the ability for renal solute transport. This leads to disturbances in sodium, potassium, and calcium transport. The increased levels of intracellular calcium lead to disruption of the actin cytoskeletal components, which in turn results in the loss of cellular polarity, loss of the brush border, impaired cellular adhesion properties, and leaking of the tight junctions. Subsequent cell death from apoptosis and necrosis results in sloughing of cells. These necrotic cells result in casts and debris which obstruct the tubules, further decreasing GFR.

The medullary thick ascending limb and the S3 segment of the proximal tubule are particularly susceptible to ischemic damage due to their high metabolic activity in a low-oxygen environment.

Certain segments of the nephron are more susceptible to oxidative damage. The medulla exists in an oxygen-poor environment. Blood is supplied to the medulla by the hairpin-shaped vasa recta, supplied by the efferent arterioles. As the vasa recta descend into the oxygen-poor medulla, oxygen diffuses into the interstitium. In the ascending portion of the hairpin, the tissue partial pressure of oxygen can be as low as 8 mm Hg. Blood flow to the medulla is less than 10% of the total renal blood flow. Although this low flow state is necessary to maintain the high interstitial osmolality required for countercurrent multiplication, the combination of low flow and low oxygen content makes the medulla highly susceptible to ischemic damage. Within the medulla, the medullary thick ascending limb is particularly susceptible to ischemic damage because it has the highest rate of sodium transport within the nephron, leading to increased oxygen requirements. Similarly, the distal portion of the proximal tubule (S3 segment), located in the outer medulla, has high metabolic activity with low oxygen under normal conditions. These segments are often the most affected during hypoxia, leading to a clinical picture of acute tubular necrosis (ATN).

The high metabolic activity and low oxygen tension in the medullary thick ascending limb have led to attempts to protect it from renal injury by reducing sodium transport and, thus, oxygen demand. There are many ways in which loop diuretics could theoretically reduce renal injury during ischemia. Increased urine output could help to wash out debris and casts, metabolic activity could be reduced due to decreased active transport secondary to the inhibition of medullary thick ascending limb Na^+-K^+-$2Cl^-$ cotransporter, and vasodilation of cortical blood vessels could improve oxygen delivery. However, despite these theoretical advantages and widespread use, clinical evidence does not support improved outcomes with the use of loop diuretics in ATN.

29.8 Acid Base

One of the main functions of the kidney is to regulate acid-base homeostasis, maintaining the intracellular pH within a narrow window. The normal values for plasma pH differ between the venous and arterial system as carbon dioxide is produced by tissue metabolism, resulting in a lower pH of the venous system. In the blood, acid is buffered by the bicarbonate system, with the following reaction representing the equilibrium which determines the free proton concentration:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

In this reaction, H^+ (the proton concentration in the blood) and HCO_3^- (the bicarbonate concentration) are in equilibrium with carbonic acid, H_2CO_3. Carbonic acid can be converted to carbon dioxide and water, catalyzed by the enzyme carbonic anhydrase. Carbon dioxide exists as a dissolved gas, and removal is regulated by the respiratory system. The concentration of H^+ in the blood is determined by this equilibrium and can be calculated using the Henderson-Hasselbalch equation:

$$pH = 6.1 + \log\left(\left[HCO_3^-\right] / \left(0.3 \times pCO_2\right)\right)$$

where $pH = -\log[H^+]$.

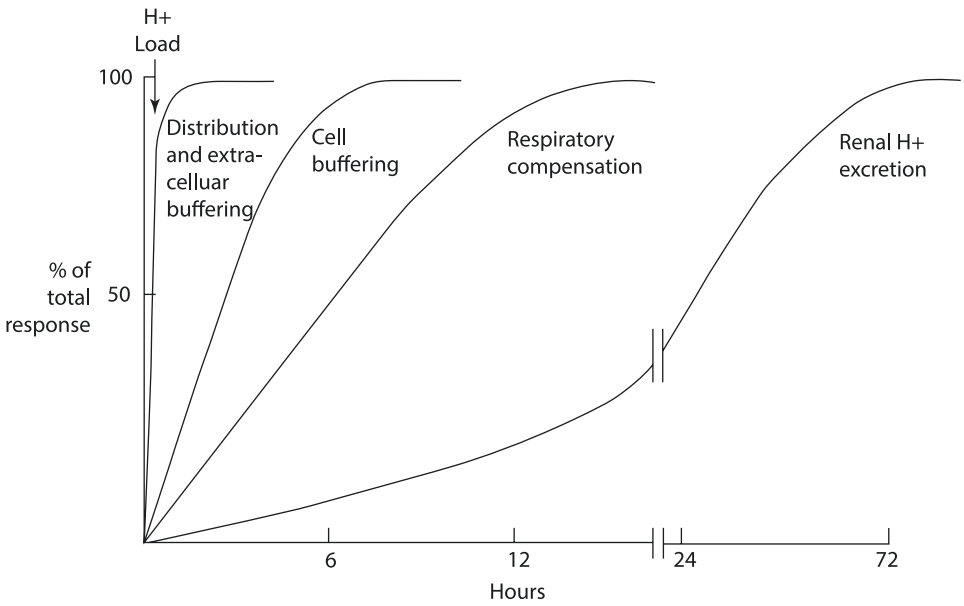
The acidity of the blood is determined by the ratio of the concentration of bicarbonate and the carbon dioxide tension. Excess acid in the blood, acidemia, occurs when there is a low pH, while an increase in serum pH is called alkalemia. In contrast, the term acidosis refers to a process which leads to an increase in the serum H^+ concentration, while alkalosis is a process which leads to a decrease in proton concentration. The maintenance of pH within a narrow range is accomplished by the combination of a complicated buffering system, respiratory adjustment of carbon dioxide tension, and renal regulation of proton secretion. A disruption of any one of these systems can result in a predictable disturbance of the serum pH.

The regulation of pH is accomplished by the combination of a complicated buffering system, respiratory adjustment of carbon dioxide, and renal regulation of proton secretion.

In the event of an acid load, the normal response involves buffering and cellular distribution, respiratory compensation, and renal hydrogen excretion. The time course for each of these mechanisms varies (◘ Fig. 29.15). In response to an acid load, there is immediate distribution of the acid and buffering by extracellular mechanisms, primarily the bicarbonate system. Within several hours, there is additional buffering from intracellular buffers such as phosphates, proteins, and hemoglobin. Bone represents another important reservoir for buffering, with as much as 40% of an acid load being buffered by bone. Skeletal muscle is an additional buffer that can be important in end-stage renal disease. Respiratory compensation, with an increase in ventilation in response to acidemia, begins within 1 hour, has a maximal response at 6–12 h, and is complete within 24 h. Renal acid excretion takes a number of days, and a maximum response may not be seen for 4–6 days. It is important to remember that the net result of renal secretion of one proton, H^+, results in the addition to the blood of a bicarbonate ion, HCO_3^-, which can then be used to buffer the daily acid load.

There are a number of sources for acid production (▶ Box 29.2), including consumption of acidic foods, metabolism of dietary products, and loss of bicarbonate in stool (◘ Fig. 29.16). Loss of bicarbonate in the stool contributes to the acid load as for each bicarbonate molecule lost, there is retention of an H^+ molecule in the extracellular fluid. Metabolism of carbohydrates and fats leads to generation of carbon dioxide, a volatile acid, which can be removed by respiration. Nonvolatile acids are formed from the metabolism of proteins. Nonvolatile

Volatile acids can be removed by respiration, while ultimately nonvolatile acids must be excreted by the kidneys as titratable acids or through ammonium generation.



◘ **Fig. 29.15** Graph depicting the time course of distribution, buffering, respiratory compensation, and renal excretion of an acid load. (Reproduced with permission from Cogan (1991))

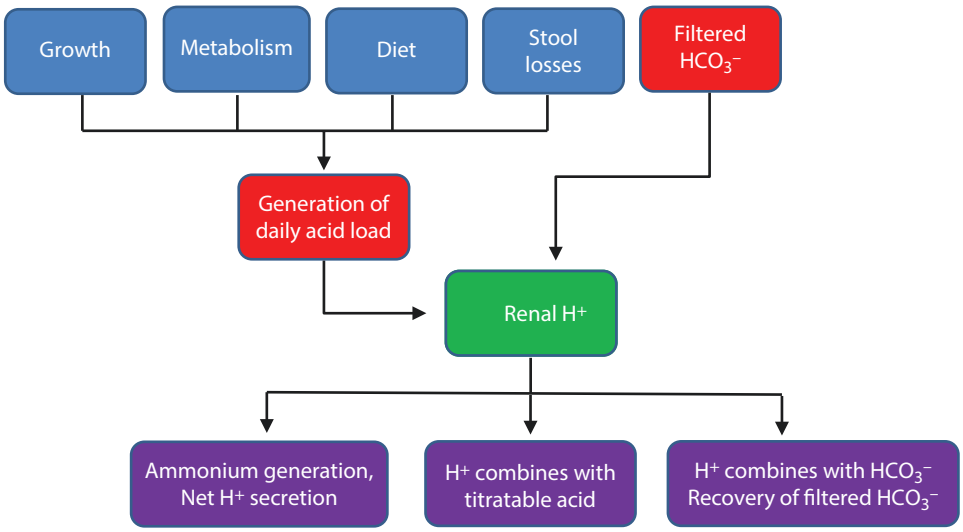


Fig. 29.16 Diagram depicting the renal regulation of acid-base balance. Acid is generated by growth, metabolism, diet, and stool losses. The kidney must reabsorb filtered HCO_3^- and excrete net acid as ammonium or titratable acid to regulate the load

acids are initially buffered in the blood but ultimately must be excreted by the kidneys in order to maintain a stable serum pH. Protons can be secreted by the kidneys as titratable acids or by generation of ammonium. Although production of an acidic urine is an important part of the process for proton secretion, the actual concentration of free H^+ molecules within the range of attainable urine pH is negligible. Under normal circumstances, the amount of endogenous acid production is relatively small (~1 mEq/kg/day), but this can increase in pathological states such as diabetic ketoacidosis. The endogenous acid load in growing children is also higher, reaching 2 mEq/kg/day.

Box 29.2 Sources of Acid Load

Sources of acid loads

1. Dietary consumption.
2. Secondary to metabolism of endogenous compounds.
3. Loss of buffer (i.e., stool bicarbonate loss).
4. Rapid growth.

In a normal adult, there is a daily acid load of about 50–100 mEq which must be excreted in order to maintain acid-base balance. In addition, in a healthy adult with a normal GFR, about 4300 mEq of bicarbonate is filtered by the kidneys and must be recovered. About 90% of the filtered bicarbonate is reabsorbed in the proximal tubule. Within the proximal tubular cell, a proton and bicarbonate are formed from water and carbon dioxide, under the action of carbonic anhydrase (Fig. 29.17). A proton, H^+, is then secreted into the lumen primarily by Na^+/H^+ exchange, with a small proportion transported by H^+ ATPase. The net result is the addition of H^+ to the lumen and HCO_3^- to the blood. H^+ in the lumen then combines with filtered bicarbonate to form water and CO_2 within the lumen. The energy for bicarbonate recovery from the cell comes from the Na^+-K^+ATPase on the basolateral membrane. Active transport of sodium out of the tubular cell lowers the intracellular sodium concentration, creating a negative potential within the cell which facilitates transport of bicarbonate out of the cell by the Na^+-$3HCO_3^-$ cotransporter. Filtered bicarbonate, which is not reabsorbed in the proximal tubule, is recovered distally in the thick ascending limb and collecting duct. In the cortical collecting duct, type A intercalated cells respond to an acid load by insertion

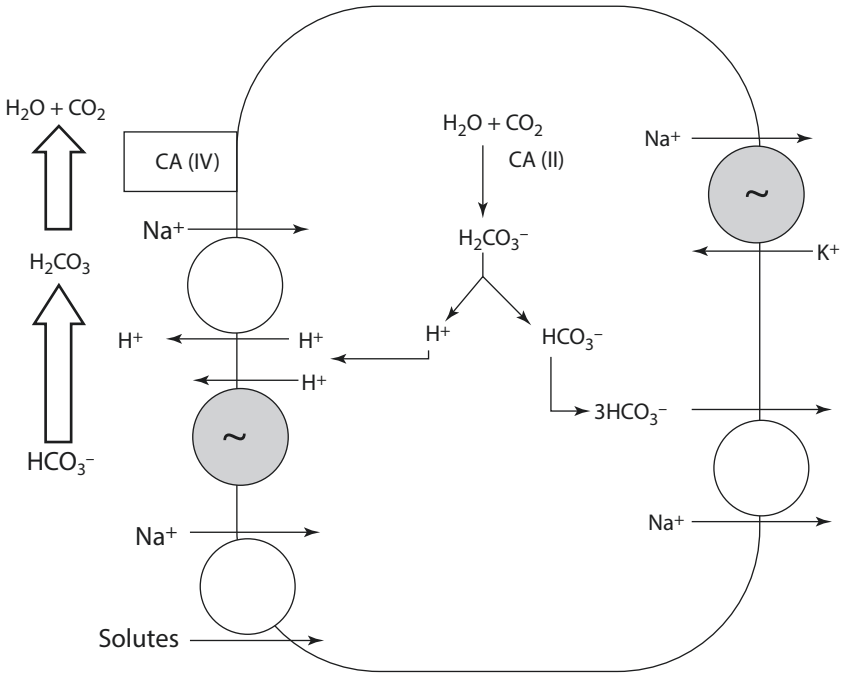


Fig. 29.17 Diagram depicting the recovery of filtered bicarbonate in the proximal tubule, which is mediated primarily by Na^+-H^+ exchange, as well as by H^+ATPase, across the apical membrane. Carbonic anhydrase along the apical membrane (*CA IV*) and in the cytosol (*CA II*) facilitates the dehydration and hydration of H_2CO_3, respectively. The bicarbonate ion that is actually reabsorbed comes from the splitting of H_2CO_3 within the cell and exits with Na^+ across the basolateral membrane via the Na^+-$3HCO_3^-$ cotransporter

CA = carbonic anhydrase

of H^+ ATPase, stored in cytoplasmic vesicles, into the luminal membrane. Bicarbonate is then transported out of the cell into the blood by a Cl^-/HCO_3^- exchanger in the basolateral membrane.

Secretion of the daily acid load can be accomplished by one of two processes: through excretion by urinary titratable acids or by secretion of ammonium (Fig. 29.16). Secretion of actual free hydrogen ions has a minimal effect since within the range of achievable urine pH, a negligible amount of the daily acid load can be secreted. There are a limited number of titratable acids which can contribute to proton secretion since acids can only work as buffers near their pKa values. The main titratable acid is phosphate ($H_2PO_4^-$), which has a pKa of 6.8. Other acids, such as creatinine and uric acid, play a minor role. Within the lumen, the addition of a proton to HPO_4^{2-} results in the formation of $H_2PO_4^-$, which can then be excreted:

$$H^+ + HPO_4^{2-} \rightarrow H_2PO_4^-$$

The ability of this buffering system is limited by the quantity of titratable acids which are present in the urine. Under normal conditions in an adult, 10–40 mEq of H^+ can be buffered by titratable acids. While this is helpful to excrete the daily acid load, there is a limited capacity to increase excretion in the event of a disturbance. One exception to this inability to increase excretion occurs in diabetic ketoacidosis, in which the generation of ketone anions, such as beta-hydroxybutyrate, can act as a titratable acid. In most conditions, the major adaptive mechanism to respond to an acid load is the generation and secretion of ammonium, which can result in the secretion of up to 300 mEq H^+/day in the face of acidosis. The production of ammonium is a complicated process which involves multiple segments of the nephron. In the early (S1) proximal tubule, ammonia (NH_3) is formed from glutamine. In the tubular lumen, the ammonia is then protonated to form ammonium (NH_4^+) (Fig. 29.18).

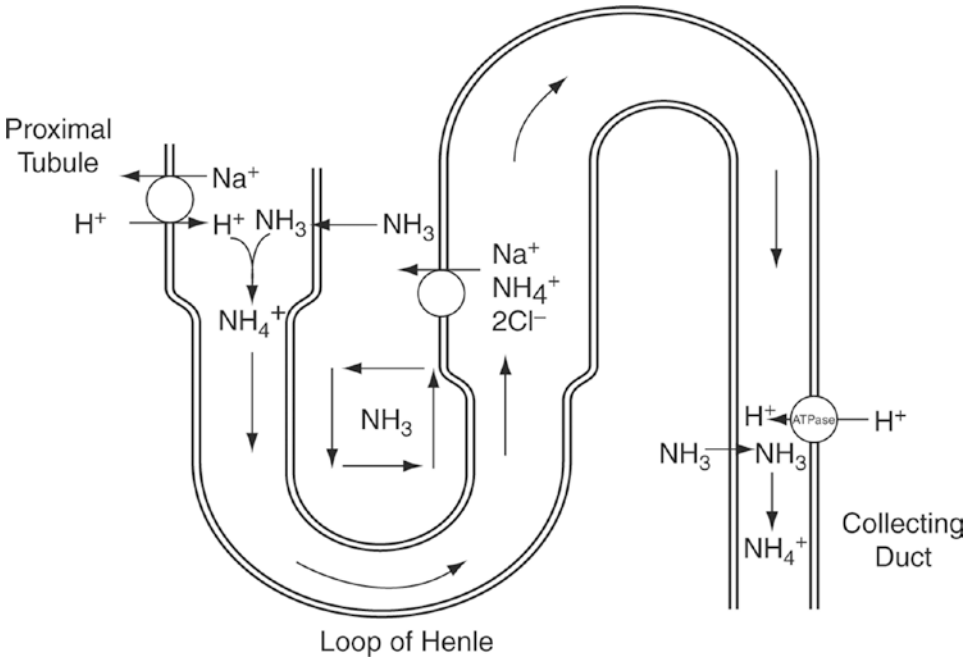


Fig. 29.18 Drawing of ammonium excretion along the nephron illustrating recycling along the limb structures and the net titration of NH_3 to NH_4^+ along the collecting duct. (Drawing by Andrew Lerner Schwartz)

While titratable acids are helpful in excreting the daily acid load, there is a limited capacity to increase excretion in the event of an acid load. The major adaptive mechanism to respond to an acid load is increased renal ammonium production.

$$NH_3(\text{ammonia}) + H^+ \leftrightarrow NH_4^+(\text{ammonium})$$

The proximal tubule is impermeable to the charged molecule, and thus, the NH_4^+ is trapped in the lumen. Within the loop of Henle, there is equilibrium between ammonia and ammonium. Through substitution in potassium channels (primarily Na^+-K^+-$2Cl^-$ cotransporter), NH_4^+ is transported into the cells of the thick ascending limb. The NH_4^+ then dissociates to a proton and NH_3. NH_3 is unable to diffuse back into the lumen because this portion of the nephron is impermeable to NH_3. Instead, NH_3 diffuses into the medullary interstitium. From there, some NH_3 is recycled back to the proximal tubule, while the rest diffuses throughout the interstitium. In the collecting duct, there is a low concentration of NH_3 within the lumen. This portion of the nephron can have a pH as low as 4.5 due to proton secretion. This favors the formation of NH_4^+ from any NH_3 within the lumen, thereby keeping the concentration of NH_3 within the lumen low. Since the collecting duct is permeable to NH_3, ammonia diffuses down a concentration gradient from the ammonia-rich interstitium into the lumen of the collecting duct. Within the lumen, the ammonia is protonated to NH_4^+ which is then excreted.

29.8.1 Regulation of Renal Hydrogen Excretion

A decreased extracellular pH, hypokalemia, and a decreased effective circulating volume can lead to an increase in renal acid excretion.

Regulation of renal hydrogen excretion is primarily in response to the extracellular pH. The kidney responds within hours to an acid load, with a complete response within 4–6 days (Fig. 29.15). Other factors which can have noticeable effects on the renal hydrogen excretion include the plasma potassium concentration and the effective circulating volume. Potassium has a direct effect on renal proton secretion, with hyperkalemia leading to decreased acid secretion and hypokalemia resulting in the opposite effect. Effective circulating volume affects acid regulation in multiple ways. First, decreased circulating volume increases the reabsorptive capacity of bicarbonate, as large quantities of sodium are being reabsorbed. Sodium reabsorption must be accompanied by an anion. Chloride is the most important reabsorbable ion.

Once chloride is depleted, in order to further reabsorb Na^+, there must be excretion of either K^+ or H^+. Thus, even if there is systemic alkalemia, there may be K^+ and proton excretion, resulting in potassium depletion and alkalosis. Chloride also has sodium-independent direct effects on renal acid-base transport that can contribute to ongoing alkalosis in the face of hypochloremia. Finally, volume depletion can increase systemic alkalosis due to activation of the renin-angiotensin-aldosterone axis, with net H^+ secretion resulting. Consequently, in a state of volume depletion with alkalosis, the best choice for fluid resuscitation may be a sodium chloride solution as it results in chloride repletion in addition to volume repletion. If chloride is not replaced, ongoing alkalosis may occur even with correction of hypovolemia or with the addition of acid.

29.8.2 Defects in Acidification

Effective regulation of acid-base status requires that the kidneys retain the ability to recover virtually all of the filtered bicarbonate, acidify the urine, and effectively excrete additional protons as ammonium. A defect in any one of these mechanisms leads to a normal anion gap acidosis known as renal tubular acidosis (RTA). RTA is classified based on the location of the defect. Distal RTA (dRTA), also known as type 1 RTA, occurs when distal acidification and H^+ secretion are impaired. Distal RTA may be inherited as an autosomal-dominant or autosomal-recessive trait. Autosomal-recessive dRTA often presents in infancy, whereas autosomal-dominant dRTA may not present until adolescence or young adulthood. Mutations in the genes encoding carbonic anhydrase II, kidney anion exchanger 1 (kAE1), and subunits of the renal proton pump (H^+ATPase) have been identified in patients with dRTA. Sensorineural deafness is often found with genetic forms of dRTA in which the vacuolar proton pump is mutated. Amphotericin B can cause an acquired dRTA which is due to increased membrane permeability within the tubular cells of the distal nephron. Distal RTA is usually associated with hypokalemia. There is one form of hyperkalemic dRTA in which reduced sodium reabsorption within the principal cells in the cortical collecting tubule leads to a voltage-dependent defect in proton secretion. This can be seen with obstructive uropathy, sickle cell disease, and severe volume depletion and with drugs which inhibit sodium reabsorption, such as lithium, trimethoprim, and amiloride.

In distal RTA, decreased urinary proton excretion leads to severe, progressive acidosis which can be accompanied by kidney stones or nephrocalcinosis.

Distal RTA results from a decrease in urinary proton excretion. This leads to a high urine pH (>5.3), ineffective generation of ammonium, and the inability to excrete an acid load. The result is a severe, progressive acidosis in which the serum bicarbonate can fall below 10 mEq/L (◘ Table 29.9). However, since proximal function is intact and the kidneys are able to recover the filtered bicarbonate, the fractional excretion of bicarbonate is low (<3% in adults, 5–10% in young children). Due to the severity of the acidosis, dRTA can present with recurrent episodes of vomiting and dehydration, poor feeding, constipation, and failure to thrive. Children frequently have kidney stones, nephrocalcinosis, and hypercalciuria. Stone formation occurs as a result of the increased calcium and phosphorus release from the bone during buffering of acidemia, decreased tubular reabsorption of calcium and phosphorus leading to hypercalciuria and hyperphosphaturia, and low levels of urinary citrate (a stone inhibitor). A final factor in stone formation is the high urine pH seen in distal RTA, which decreases the solubility of calcium phosphate, increasing the likelihood of stone formation. Growth retardation is usually prominent. Hypokalemia, when present, can lead to severe muscle weakness. Distal RTA

Table 29.9 Typical features of renal tubular acidosis (RTA)

	Distal RTA (type1)	Proximal RTA (type2)	Aldosterone deficiency/ resistance (type 4)
Serum potassium	Normal/low	Normal/low	High
	High with voltage defect		
Urine pH when acidotic	>5.3	Variable (< 5.3 when below threshold)	<5.3
Serum bicarbonate (untreated)	Low (can be <10 mEq/L)	14–20 mEq/L	>15 mEq/L
Fractional excretion of bicarbonate with normal serum bicarbonate	<3% (adults)	>15–20%	<3%
	<5–10% (young children)		
Associated conditions	Nephrocalcinosis	Rickets Failure to thrive Recurrent vomiting	
	Renal stones		
Clinical course	Usually requires lifelong therapy	Can be transient	Variable, depends on underlying cause

Adapted from Rose and Post (2001)

is almost always permanent, requiring lifelong treatment with an alkalinizing agent.

Proximal RTA (pRTA), also known as type 2 RTA, is due to decreased capacity of the proximal tubule to reabsorb the filtered load of bicarbonate. As bicarbonate is lost in the urine, the serum bicarbonate falls, leading to a decrease in the amount of bicarbonate which is filtered. At some point, a threshold is reached where the proximal tubule is able to reabsorb the remaining bicarbonate, and the serum bicarbonate stabilizes at a new steady state, usually at a level of 14–20 mEq/L. This can be demonstrated by determining the fractional excretion of bicarbonate in the face of bicarbonate loading. As serum bicarbonate increases above the threshold, spilling of bicarbonate in the urine results in a fractional excretion which is greater than 15–20%. Although huge amounts of bicarbonate may be lost, distal function is intact so the ability to acidify the urine is retained once a steady state has been reached. Thus, despite a low serum pH, the urine pH can be less than 5.3. Features of pRTA include growth retardation, recurrent vomiting, and failure to thrive. Unlike distal RTA, proximal RTA is rarely associated with stones or nephrocalcinosis. Rickets and osteomalacia may occur in association with phosphate wasting. The proximal dysfunction of type 2 RTA can be accompanied by generalized proximal dysfunction, which is also known as Fanconi syndrome. In Fanconi syndrome, there can be loss of glucose, amino acids, potassium, uric acid, and phosphorus in the urine in addition to the bicarbonate wasting.

Idiopathic pRTA may be due to mutations in the genes coding for the Na^+-$3HCO_3^-$ cotransporter. Acquired forms may be due to carbonic anhydrase inhibition by acetazolamide or topiramate leading to bicarbonate wasting or

nephrotoxic conditions such as cystinosis or drugs such as ifosfamide affecting the reabsorption of bicarbonate and other proximal tubule solutes resulting in a proximal Fanconi syndrome.

Therapy for pRTA often requires large amounts of bicarbonate (10–15 mEq/kg/day) because increasing levels of serum bicarbonate result in a filtered load that is above the reabsorptive capacity, and most is lost in the urine. In addition, if there is phosphate wasting and bone disease, phosphate and vitamin D supplementation may be required. We have also supplemented pRTA patients with L-carnitine, which is wasted in the full renal Fanconi syndrome. Isolated, idiopathic pRTA in children, particularly in males, may be transient, resolving within a few years.

In proximal RTA, loss of filtered bicarbonate leads to a milder acidosis; however, it is difficult to treat, requiring massive doses of bicarbonate.

Type 3 RTA is rarely used as a classification because it has been found to be a combination of proximal (type 2) and distal (type 1) RTA and is unique to infants. Type 4 RTA is usually caused by insufficient aldosterone synthesis or resistance to aldosterone. Aldosterone resistance often stems from a defect in the receptor or from tubular damage. Type 4 RTA may be isolated or occur in patients with renal parenchymal disease. It may be transient in infancy and early childhood. Typically, acidosis is mild, with a serum bicarbonate >15 mEq/L. Proximal bicarbonate recovery is intact, so the fractional excretion of bicarbonate is low. Inherited defects leading to type 4 RTA include congenital adrenal hyperplasia with salt wasting, isolated hypoaldosteronism, and pseudohypoaldosteronism (due to a defect at the aldosterone receptor level). An acquired type 4 RTA can be due to tubular damage resulting from obstructive nephropathy, tubulointerstitial nephritis, sickle cell disease, kidney transplant rejection, lupus nephritis, and such drugs as cyclosporine. This is distinguished from the hyperkalemic form of dRTA by the ability to reduce the urine pH. The lack of aldosterone action results in an inability to effectively secrete protons and potassium, leading to acidosis and hyperkalemia. In addition, the accompanying hyperkalemia directly impairs ammonia production. The hyperkalemia is often out of proportion to the degree of renal impairment. The clinical presentation of type 4 RTA is varied and depends on the degree of hyperkalemia and whether salt wasting is present. Type 4 RTA is diagnosed by measuring serum aldosterone and renin levels, although some forms involve resistance to aldosterone (pseudohypoaldosteronism). Treatment depends on the underlying cause. In the case of aldosterone deficiency, mineralocorticoid replacement can result in correction of both the hyperkalemia and the acidosis.

Type 4 RTA is usually caused by insufficient aldosterone synthesis or resistance to aldosterone. Lack of aldosterone action results in an inability to effectively secrete protons and potassium, leading to acidosis and hyperkalemia.

If a diagnosis of renal tubular acidosis is suspected, there are a number of relatively simple tests which are useful as the first steps in the investigation. When RTA is suspected, the first step is simultaneous measurement of blood and urine pH. Evaluation of serum pH with a blood gas allows for confirmation that there is in fact systemic acidemia rather than a respiratory disturbance with metabolic compensation. Measurement of serum electrolytes, including Na, K, Cl, HCO_3, BUN, and creatinine, allows for detection of renal insufficiency and hyperkalemia/hypokalemia and calculation of the anion gap to confirm a normal anion gap acidosis. The serum anion gap can be calculated from the following equation:

$$\text{Anion gap} = Na^+ - \left(Cl^- + HCO_3^-\right)$$

Normally, unmeasured anions result in an anion gap of 5–11 mEq/L. With renal or stool losses of $NaHCO_3$, there is increased renal reabsorption of NaCl in order to maintain extracellular volume. The result is an elevation of serum Cl^- without an elevation of the anion gap (since both Na^+ and Cl^- increase, resulting in a normal anion gap hyperchloremic metabolic acidosis). If there is

With renal or stool losses of $NaHCO_3$, increased renal reabsorption of NaCl leads to a non-anion gap hyperchloremic metabolic acidosis.

an elevated anion gap, this implies that an unmeasured anion is contributing to the acidosis, and this should be investigated further.

Close examination of the urine can provide additional information which is useful in the evaluation of RTA. Urine pH can be helpful in differentiating between the different types of RTA, but it is important to remember that a low urine pH is not inconsistent with RTA. Urinalysis, urine electrolytes, and urine amino acid evaluation allow for detection of glucosuria, phosphaturia, and aminoaciduria and evaluation of urinary sodium handling. Urine electrolytes can be used to calculate the urine net charge, which gives an estimate of urinary ammonium excretion:

$$\text{Urine net charge (mEq/L)} = \text{urine } Na^+(U_{Na}) + \text{urine } K^+(U_K) - \text{urine } Cl^-(U_{Cl})$$

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Since the major cation which is not measured is ammonium, the urine net charge is indicative of urinary ammonium excretion. In the case of systemic acidemia, the appropriate renal response is ammonium generation to allow for excretion of the acid load. In this case, a large number of Cl^- ions should be present to balance the unmeasured cation ammonium, leading to a negative urine net charge, typically −30 to −50 mEq/L. Confirmation of a negative urine net charge is consistent with intact distal urinary acidification mechanisms. If there is a normal anion gap with a negative urine net charge, distal acidification is occurring and the differential diagnosis includes pRTA, acetazolamide use, and other sources of bicarbonate loss such as stool losses. A urine net charge that is positive (>0 mEq/L) implies low distal acidification and is consistent with renal causes of acidosis such as dRTA and type 4 RTA. In order to evaluate the urine net charge, there must be adequate distal sodium delivery with a urine sodium >25 mEq/L. Low distal sodium delivery, such as occurs with hypovolemia, causes a reversible form of dRTA which will correct with volume repletion as sodium delivery to the distal segment increases.

Low distal sodium delivery, such as occurs with hypovolemia, causes a reversible form of dRTA which will correct with volume repletion as sodium delivery to the distal segment increases.

The urine net charge is not a useful tool when there are unmeasured anions present, such as in ketoacidosis or with drugs which are excreted as anions, such as penicillin and aspirin. The urine net charge may not be useful in the neonatal intensive care unit due to the unmeasured anions. In these situations, the amount of ammonium may be estimated by examining the urine osmolal gap, comparing the calculated and measured urine osmolality (U_{osm}). Since ammonium salts (NH_4^+ and its associated anion) represent the major unmeasured osmoles, the amount of ammonium can be estimated by using the following equation:

$$\text{Urine } NH_4^+ = \tfrac{1}{2}\left(\text{Measured } U_{osm} - \text{Calculated } U_{osm}\right)$$

If U_{Na} and U_K are in mEq/L but U_{urea} and U_{glu} are in mg/dL, the following equation can be used to convert all variables to mmol/L:

$$\text{Urine } NH_4^+ \left(\text{mmol/L}\right) = \frac{\left[U_{osm} - \left(2 \times U_{Na} + 2 \times U_K + U_{urea}/2.8 + U_{glu}/18\right)\right]}{2}$$

Since NH_4^+ salts are the major unmeasured osmoles in the urine, the osmolal gap is reflective of urine ammonium excretion. If there is systemic acidemia, the appropriate renal response is generation of ammonium with a urinary ammonium value greater than 75 mmol/L. A urine NH_4^+ which is less than 25 mmol/L is consistent with RTA with inadequate ammonium production.

29.8.3 Treatment of RTA

The type of treatment for RTA is beyond the scope of this chapter but generally involves the administration of an alkalinizing agent as well as therapy to address other electrolyte disturbances. In all cases of RTA in children, in order to maximize growth and function, the goal should be to raise the serum bicarbonate to at least 20–22 mEq/L. Doses of bicarbonate as high as 15 mEq/kg/day may be required, particularly in pRTA, because large amounts of bicarbonate can be lost in the urine once the serum bicarbonate is raised above the threshold. The two options for chronic therapy include bicarbonate and citrate supplementation. Sodium bicarbonate is effective therapy and corrects acidosis caused by any form of RTA. A preferred alternative is citrate of sodium or potassium. Citrate is converted by the liver to bicarbonate. Citrate is more palatable than bicarbonate and is not associated with bloating and belching. Potassium citrate does not result in the volume expansion caused by sodium salts, which becomes very important in the treatment of pRTA. Hypokalemia observed in conjunction with pRTA or dRTA may improve with treatment of the acidosis or may require additional supplementation. Hyperkalemia may need to be treated acutely in type 4 RTA with loop diuretics. In type 4 RTA in which there is aldosterone deficiency or resistance, additional therapy with a mineralocorticoid such as fludrocortisone may be necessary.

In all cases of RTA in children, in order to maximize growth and function, the goal should be to raise the serum bicarbonate to at least 20–22 mEq/L.

29.8.4 Lactic Acidosis

Lactic acidosis is a relatively common form of metabolic acidosis in hospital-associated conditions with an elevated serum anion gap and lactate level exceeding 4 mmol/L. Increased lactate levels are usually associated with impaired tissue oxygenation either from reduced oxygen delivery or from a defect in cell utilization of mitochondrial oxygen. Shock is a major form of tissue hypoperfusion resulting from hypovolemia, cardiac arrest/failure, or sepsis, and the prognosis is poor unless tissues can be reperfused. Other forms of lactic acidosis are not associated with tissue hypoperfusion such as diabetes mellitus with ketoacidosis and a variety of congenital or acquired mitochondrial defects that impair pyruvate utilization. Cases of lactic acidosis have also been reported with high doses of the sedative propofol and with the antibiotic linezolid. Rarely in patients with short gut or malabsorptive syndromes, a form of D-lactic acidosis develops from the fermentation of sugar and starch by intestinal bacteria. Bicarbonate use in the treatment of lactic acidosis is controversial.

Review Questions

1. In which segment of the nephron is 80% of filtered bicarbonate recovered?
   A. Collecting duct.
   B. Distal tubule.
   C. Proximal tubule.
   D. Thick ascending loop of Henle.
   E. Thin descending loop of Henle.

2. Which of the following is true regarding creatinine as a measure of renal function?
   A. Creatinine secretion into the ultrafiltrate is clinically insignificant.
   B. In a normal kidney, creatinine clearance underestimates GFR by 10–20%.
   C. Plasma creatinine reaches adult levels shortly after the second year of life.

D. Plasma creatinine is unaffected by diet.
E. There can be as much as a 50% decrease in nephron mass prior to any detectable increase in serum creatinine.

3. Which hormone regulates serum osmolality by controlling the insertion of water channels into the luminal membrane of the principal cells of the collecting ducts?
   A. Aldosterone.
   B. Antidiuretic hormone (ADH).
   C. Atrial natriuretic peptide (ANP).
   D. Erythropoietin.
   E. Leptin.

4. A 3-month-old, former premature male infant with bronchopulmonary dysplasia is noted to have nephrocalcinosis on renal ultrasound. Analysis of the urine reveals hypercalciuria. Which of the following diuretics has he most likely received on a long-standing basis?
   A. Chlorothiazide.
   B. Furosemide.
   C. Mannitol.
   D. Metolazone.
   E. Spironolactone.

5. A 3-year-old, recently adopted child with failure to thrive and suspected rickets is noted to have mild but persistent metabolic acidosis with bicarbonate values 15–18 mEq/L. His urine pH on initial evaluation was 5.0. Although his bicarbonate level is only mildly decreased, he is requiring massive doses of bicarbonate to increase these levels. After his serum bicarbonate levels have increased, analysis of his urine reveals a fractional excretion of bicarbonate of 20%. Which of the following is the most likely explanation for his metabolic acidosis?
   A. Acidosis due to stool bicarbonate loss.
   B. Distal renal tubular acidosis (RTA).
   C. Post-hypocapnic acidosis.
   D. Proximal RTA.
   E. Type IV RTA.

6. An 18-month-old female is admitted with vomiting and diarrhea of 2 days duration. Her vital signs are temperature 38.5 °C, pulse 148 beats per minute, blood pressure 85/52 mm Hg, and respiratory rate of 38 breaths per minute. Clinical exam reveals a lethargic but responsive child with dry mucous membranes. She has palpable although thready pulses, with tepid distal extremities to touch and a 4-second capillary refill. Laboratory evaluation reveals a blood urea nitrogen (BUN) level of 32 mg/dL and a serum creatinine concentration of 0.9 mg/dL. Which of the following is true regarding her elevated urea level?
   A. Blood urea is increased during hypovolemia mainly due to hemoconcentration.
   B. Blood urea is increased during hypovolemia mainly due to increased reabsorption.
   C. Urea is freely filtered at the glomerulus and undergoes little reabsorption.
   D. Urea production is decreased during critical illness.
   E. Urea production is increased during states of increased anabolism.

7. A two-year-old male is transferred to the pediatric intensive care unit from a referring institution with hypotension secondary to severe diarrhea and dehydration. His mother reports he has had diarrhea and fever for 4 days. He has had oral hydration with a pediatric rehydration solution and an appropriate dose of ibuprofen for fever every 6 hours. Vital signs are pulse 167 beats per minute, blood pressure 109/67 mm Hg, and respiratory rate of 44 breaths per minute. Examination reveals a lethargic child with cool extremities, delayed capillary refill, and dry mucous membranes. Laboratory evaluation reveals:
   Sodium: 141 mEq/L
   Chloride: 121 mEq/L
   Potassium: 5.9 mEq/L
   BUN: 44 mg/dL
   Creatinine: 4.2 mg/dL
   Bicarbonate: 7 mEq/L
   Which of the following is most true regarding his decrement in renal function?
   A. His BUN:creatinine ratio is reflective of hypovolemia and not acute kidney injury.
   B. His increase in creatinine is likely secondary to hemoconcentration.
   C. His increase in creatinine is reflective of a 25% reduction in GFR.
   D. The acidosis is likely due to renal injury and renal loss of bicarbonate.
   E. The use of ibuprofen likely impaired the ability of the kidney to compensate for decreased perfusion.

8. A 19-month-old, 12.8 kg male infant is recovering from sepsis-induced acute respiratory distress syndrome. He is receiving furosemide in an attempt to improve his fluid excretion and facilitate weaning of his mechanical ventilation support. Despite this therapy, he remains in positive fluid balance. A decision is made to add a thiazide diuretic to augment his urine output. Which of the following statements is true regarding the use of a thiazide diuretic in this setting?
   A. Thiazide diuretics do not increase the potency of loop diuretics as is commonly believed.
   B. Thiazide diuretics increase the potency of loop diuretics by blocking the flow-dependent increase in sodium reabsorption in the distal tubule.
   C. Thiazide diuretics increase the potency of loop diuretics by inducing a diabetes insipidus-like physiology via their effect on the aquaporin-2 water channels.
   D. Thiazide diuretics provide a potassium-sparing effect minimizing the potential for hypokalemia with loop diuretics by functionally inhibiting aldosterone.
   E. Thiazide diuretics should not be used in conjunction with loop diuretics because they decrease the reabsorption of calcium and may worsen hypercalciuria.

9. A 3-year-old male is admitted with pneumococcal sepsis and severe edema secondary to nephrotic syndrome. In an attempt to optimize his care, you wish to estimate his glomerular filtration rate (GFR). Given the following information:
   Dry weight: 12 kg
   Height: 85 cm
   Plasma creatinine: 1 mg/dl
   Urine output: 2 mL/kg/hr.

Which of the following is the most accurate estimate of his GFR?

A. 10 mL/min/1.73 m^2
B. 25 mL/min/1.73 m^2
C. 30 mL/min/1.73 m^2
D. 35 mL/min/1.73 m^2
E. An estimated GFR cannot be calculated with the above data.

Answers

1. C
2. E
3. B
4. B
5. D
6. B
7. E
8. B
9. D

Suggested Reading

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Fluid/Electrolyte/Acid-Base Abnormalities

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Contents

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Learning Objectives

- Identify the major causes of dehydration.
- Identify specific therapies for dehydration disease processes focusing on rehydration of the dehydrated patient.
- Classify the causes of hypernatremia.
- Differentiate between potential therapies of hypernatremia.
- Describe the pathophysiology, diagnosis, and treatment of patients with diabetes insipidus.
- Classify the causes of hyponatremia.
- Differentiate between potential therapies of hyponatremia.
- Summarize the pathophysiology, diagnosis, and treatment of patients with SIADH.
- Summarize the pathophysiology, diagnosis, and treatment of patients with cerebral salt wasting.
- State the inherited causes of hypocalcemia and their potential treatment.
- State the causes of acquired hypocalcemia.
- Discuss the clinical signs associated with hypocalcemia.
- Discuss the treatment of hypocalcemia including when it is necessary to treat.
- Discuss the normal "handling" of and requirements for potassium in the pediatric patient.
- Recognize that because of the predominantly intracellular location of potassium, serum potassium is not a reliable indicator of total body potassium.
- Discuss the potential clinical effects associated with a low serum potassium.
- Discuss the treatment of a low serum potassium in the PICU patient including when it is necessary to treat.
- Discuss the causes and management of hypokalemia (total body potassium deficiency) in the PICU patient.
- Identify groups of patients who are at risk for hyperkalemia.
- Describe the potential ill effects associated with a high serum potassium.
- State the ECG changes associated with hyperkalemia and describe how to use the ECG to diagnose increased serum potassium.
- Describe the short-term and long-term treatment of hyperkalemia.
- Describe the clinical correlates of high and low serum magnesium.
- Define the treatment of hypomagnesemia.
- Describe the clinical correlates of high and low serum phosphorus.
- Define the treatment of hypo- and hyperphosphatemia.
- Describe the pathophysiologic effects caused by metabolic acidosis.
- Describe the basis for classifying metabolic acidosis by:
  - Acute versus chronic.
  - Presence or absence of abnormally large anion gap.
- Formulate the differential diagnosis for each of the above subgroups.
- Describe the arguments for and against the treatment of metabolic acidosis with bicarbonate for each of the groups described above.
- Summarize the pathophysiologic effects caused by metabolic alkalosis.
- Identify the major causes of acute and chronic metabolic alkalosis.
- Describe the general treatment of metabolic alkalosis including when acute treatment is indicated.

30.1 Volume Depletion (Dehydration)

Volume depletion, commonly referred to as dehydration, occurs whenever water and salt losses exceed intake. If oral intake remains adequate, dehydration is usually avoided. Infants are especially prone to dehydration because they have higher proportional body fluid turnover than older children or adults. If an infant develops anorexia or vomiting, dehydration develops sooner than in the older child because of the higher proportion of obligatory losses. Diarrhea in conjunction with vomiting is the most common cause of dehydration in children. Dehydration can also occur from increased sweating produced by fever; acute infections that decrease oral intake, such as pneumonia or meningitis; or conditions that cause increased renal losses of salt and water such as pyelonephritis or excess diuretic use.

The clinical signs of dehydration are a manifestation of extracellular volume depletion. Signs of extracellular volume depletion in children include an elevation in heart rate, delayed capillary refill, diminished tearing, dry mucous membranes, a sunken fontanel, poor skin turgor, decreased peripheral pulses, cool peripheries, and ultimately a fall in blood pressure when volume depletion is severe. Three factors determine the amount of extracellular volume depletion and therefore the severity of dehydration: (1) the fluid deficit, (2) the electrolyte deficit, and (3) the speed at which dehydration occurs.

The fluid deficit or antecedent deficit is the total amount of body water lost. It is expressed as the percent decrease in body weight and can be estimated based on physical findings (Table 30.1). In general, the larger the fluid deficit, the more severe the degree of dehydration. The clinical signs of dehydration are also affected by the electrolyte deficit, which usually parallels extracellular fluid losses. Therefore, for the same fluid deficit, the severity of clinical signs of extracellular volume depletion is inversely proportional to the serum sodium concentration. Stated differently, given the same volume loss, hyponatremic dehydration is clinically more severe than hypernatremic dehydration. Signs of volume depletion are less pronounced in patients with hypernatremia due to better preservation of the extracellular volume. This is the basis for classifying dehydration according to the serum sodium as hyponatremic, isonatremic, or hypernatremic. The rate at which dehydration occurs also affects the severity of extracellular volume depletion. Initial fluid losses typically come primarily from the intravascular space. Over time, fluid is mobilized from the interstitial and intracellular space to maintain intravascular volume. If fluid depletion of the intravascular space occurs rapidly, this compensatory process is less complete, and signs of intravascular volume depletion predominate. Therefore, dehydration occurring over several days to a week is better tolerated than dehydration occurring over hours or a day.

The most important determinant of serum sodium concentration in the presence of dehydration is the type and volume of fluid intake.

The most common cause of dehydration in children is infectious diarrhea, particularly rotavirus. The diarrheal losses are usually hypotonic to serum; stool [Na and K] is between 80 and 130 mEq/L. The most important factor in determining the type of dehydration is the amount and type of oral intake. In most instances, the amount of free water losses and free water ingested are of similar magnitude, resulting in little change in serum sodium. In infants where water intake may be decreased due to limited access or vomiting, free water losses result in hypernatremic dehydration. In older children who may be able to satisfy their thirst or who are taking very hypotonic oral fluids, free water intake in excess of free water losses results in hyponatremic dehydration.

Table 30.1 Clinical signs of dehydration

	Mild	Moderate	Severe
Weight loss	3–5%	6–9%	>10%
Skin turgor	Normal	Tenting	None
Skin: Touch	Normal	Dry	Clammy
Capillary refill (s)	<2	>2	>2
Mucous membranes	Moist	Dry	Parched
Eyes	Normal	Intermediate	Sunken
Tears	Present	Absent	Absent
Pulse	Full	Decreased	Weak or absent
Heart rate	Regular	Rapid	Rapid
Blood pressure	Normal	Normal–low	Hypotensive shock
Urine output	Decreased	Oliguria	Anuria
Fontanel (if present)	Normal	Sunken	Markedly sunken
Sensorium	Clear	Lethargic	Listless

30.1.1 Treatment

The primary goal of rehydration is to reestablish hemodynamic stability and tissue perfusion. In severe dehydration with hemodynamic compromise, very rapid administration of 20–40 mL/kg of an isotonic solution, such as 0.9% sodium chloride, Plasma-Lyte, lactated Ringer's, or Hartmann's solution, is warranted. Further fluid resuscitation should continue until the child is hemodynamically stable. This requires close serial examination of distal perfusion, measurement of urinary output, and analysis of serum chemistries to guide ongoing fluid replacement. Volume depletion can generally be corrected by administering 40 mL/kg of an isotonic solution over 2–4 h, followed by the remainder of the deficit and ongoing maintenance as 0.9% sodium chloride with appropriate amounts of dextrose and potassium added. Hypotonic fluids such as 0.45% and 0.22% sodium chloride have no role in the initial therapy of a volume-depleted child. Hypotonic fluids may be necessary after the initial phase of fluid therapy if there is hypernatremia, ongoing free water losses from high fever or voluminous diarrhea, or a renal concentrating defect such as congenital nephrogenic diabetes insipidus or renal dysplasia. Hypotonic fluids may also be required in a child with severe hyponatremic dehydration after initial therapy with 0.9% sodium chloride to prevent rapid correction of hyponatremia from a free water diuresis.

30.1.1.1 Isotonic Solution Versus Balanced Solution for Fluid Resuscitation

There has been a growing concern that 0.9% saline has a supraphysiological chloride concentration and may result in untoward complications such as hyperchloremic metabolic acidosis, renal vasoconstriction, delayed micturition, hyperkalemia, an increased incidence of acute kidney injury, and need for renal replacement therapy. The benefit of balanced solutions over isotonic saline seems to be primarily in critically ill adult patients with sepsis and those with preceding acute kidney injury and previous renal replacement therapy. It

Isotonic solutions should be used for parenteral volume expansion in the dehydrated child.

Hypotonic fluids should not be administered rapidly to a dehydrated child. Slow correction of hypernatremia may require the judicious use of hypotonic fluids to correct free water losses.

is unclear if this is applicable to children with volume depletion. Balanced solutions differ from normal saline primarily in having variable amounts of a buffering agent, such as lactate, acetate, or gluconate. Balanced solutions do not have bicarbonate as it is not stable in polyvinyl chloride bags. Balanced solutions also have variable amounts of potassium, calcium, and magnesium and have a lower sodium concentration and osmolarity in comparison to normal saline (Table 30.2). A 0.9% saline solution (Na 154 mmol/L) has a higher sodium concentration than plasma but results in normal osmolarity, whereas Plasma-Lyte (Na 140 mmol/L) and lactated Ringer's (Na 130 mmol/L) are slightly hypotonic in relationship to plasma. Lactated Ringer's in particular may aggravate hyponatremia and should be avoided in hyponatremic patients or those at high risk for cerebral edema.

30.2 Hypernatremia

Hypernatremia is defined as a serum sodium >145 mEq/L. Hypernatremia occurs in children and adults often in the presence of restricted access to water for a variety of reasons. In most instances, these patients either are debilitated by an acute or chronic illness or neurologic impairment or are at the extremes of age. Hypernatremia is also not uncommon in children in the intensive care unit. Contributing factors for hypernatremia in the intensive care setting are excess sodium administration, renal concentrating defects, gastrointestinal fluid losses, increased insensible water losses, restricted access to oral fluids, and dialysis-related complications. Excess administration of sodium can occur via hypertonic solutions, blood products, and sodium bicarbonate administration. Increased insensible water losses occur with fever, tachypnea, and burns. Hypernatremia can result from intentional salt poisoning, in particular in children with gastrostomy tubes. A serum sodium greater than 145 mEq/L should always be considered abnormal and evaluated thoroughly in order to prevent the development of significant hypernatremia.

30.2.1 Pathogenesis

The body has two defenses to protect against developing hypernatremia: the ability to produce concentrated urine by reabsorbing filtered water and a powerful thirst mechanism. Antidiuretic hormone (ADH) release occurs when the plasma osmolality exceeds 275–280 mOsm/kg and results in a maximally concentrated urine when the plasma osmolality exceeds 290–295 mOsm/kg. Thirst is the body's second line of defense but provides the ultimate protection against hypernatremia. If the thirst mechanism is intact and there is unrestricted access to free water, it is rare for someone to develop sustained hypernatremia from either excess sodium ingestion or a renal-concentrating defect.

30.2.2 Diagnosis

Less than maximally concentrated urine (<800 mOsm/kg) in a hypernatremic patient signifies a renal concentrating defect.

The cause of hypernatremia is usually multifactorial and a systematic approach is required to determine the underlying etiology (Fig. 30.1). Serum sodium, glucose, and osmolality must be simultaneously evaluated. Elevated serum sodium is always associated with hyperosmolality and should be considered abnormal. In association with significant hyperglycemia, the serum sodium concentration is depressed due to the associated translocation of fluids from the

Table 30.2 Composition of commonly used resuscitation fluids

Fluid	Sodium mEq/L	Chloride mEq/L	Potassium mEq/L	Calcium mEq/L	Magnesium mEq/L	Buffer mEq/L	Osmolarity mOsm/L	Osmolality mOsm/kg[a]
Human plasma	135–144	95–105	3.5–5.3	4.4–5.2	1.6–2.4	23–30 bicarbonate	308	287[b]
Normal saline								
0.9% NaCl	154	154	0	0	0	0	308	287
Balanced solutions								
Hartmann's	131	111	5	4	0	29 lactate	278	256
Lactated Ringer's	130	109	4	3	0	28 lactate	273	254
Plasma-Lyte	140	98	5	0	3	27 acetate and 23 gluconate	294	273

[a]Calculated osmolality = (0.93 X osmolarity)
[b]The range of osmolality for plasma is 275–295 mOsm/kg

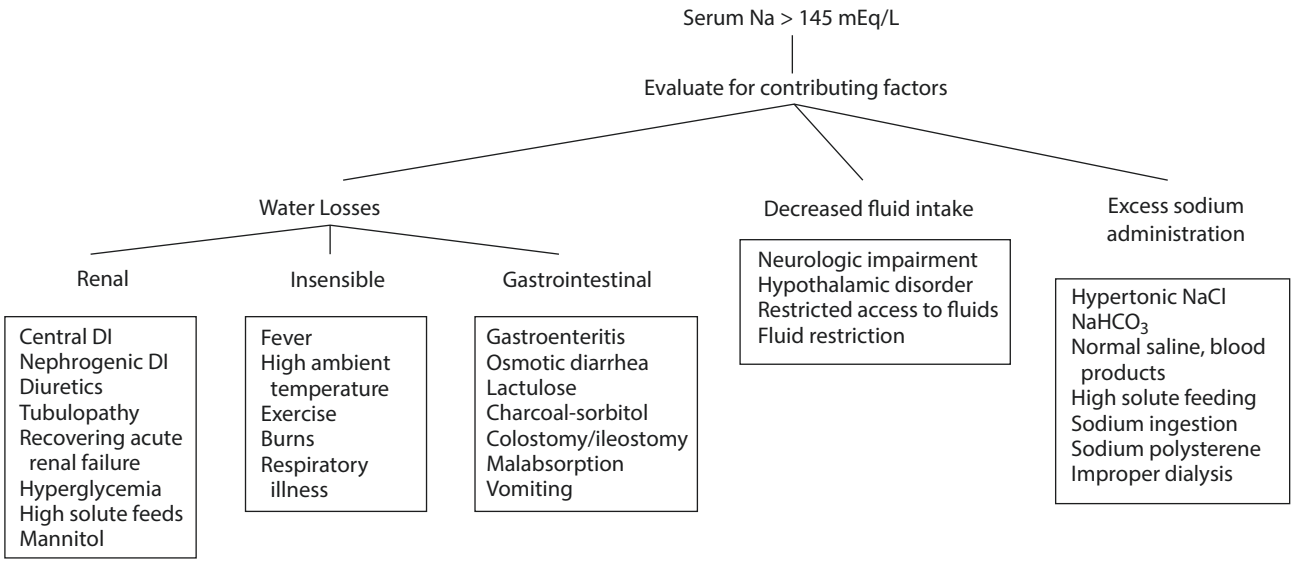

Fig. 30.1 Diagnostic approach to hypernatremia

intracellular to extracellular space, and therefore, true hypernatremia will be masked. Once the diagnosis of hypernatremia is established, a detailed history and review of fluid intake should be obtained to determine if the patient has an intact thirst mechanism, had restricted access to fluids, or was not provided adequate free water in intravenous fluids. The following should be evaluated: gastrointestinal losses, urinary output, dermal losses from fever or burns, diet history (including tube feedings), medication history (including diuretics), and sources of exogenous sodium. Urine volume should be measured and compared to fluid intake. The urine osmolality and electrolytes should be determined to assess if the renal concentrating ability is appropriate and to quantify the urinary free water losses. Less than maximally concentrated urine (<800 mOsm/kg) in the face of hypernatremia associated with signs of dehydration is a sign of a renal concentrating defect as hypernatremia is a maximal stimulus for ADH release. A useful test for distinguishing central from nephrogenic diabetes insipidus is plasma copeptin testing. Copeptin, the C-terminal segment of the pre-pro-hormone for arginine vasopressin, can be used as a surrogate marker of ADH as it is easier and more reliable to measure than ADH. Salt poisoning should be considered in cases of severe and unexplained hypernatremia. A gastric or stool sodium concentration higher than plasma sodium is virtually diagnostic of salt poisoning. Pseudohypernatremia has been reported to occur with vecuronium and esmolol due to interference with ion-selective electrodes.

30.2.3 Clinical Manifestations of Hypernatremia

Hypernatremia results in an efflux of fluid from the intracellular space to the extracellular space to maintain osmotic equilibrium. This leads to transient cerebral dehydration with cell shrinkage. Brain cell volume can acutely decrease by as much as 10–15% but then quickly adapts. In response to extracellular hyperosmolarity, within 1 hour, brain cells significantly increase their intracellular content of sodium and potassium, amino acids, and unmeasured organic substances called idiogenic osmoles. Within 1 week, brain cells regain approximately 98% of their water content. If severe hypernatremia develops acutely, the brain may not be able to increase its intracellular solute sufficiently to pre-

serve its volume, and the resulting cellular shrinkage can cause structural changes. Cerebral dehydration from hypernatremia can result in functional changes and a physical separation of the brain from the meninges leading to a rupture of the delicate bridging veins and extra-axial or intracerebral hemorrhages. Venous sinus thrombosis leading to infarction can also develop. Acute hypernatremia has also been shown to cause cerebral demyelinating lesions in both animals and humans. Patients with hepatic encephalopathy are at the highest risk for developing demyelinating lesions, especially if hypernatremia is a result of rapid overcorrection of preexisting hyponatremia.

Children with hypernatremia are usually agitated and irritable but can progress to lethargy, listlessness, and coma. On neurologic examination, they frequently have increased tone, nuchal rigidity, and brisk reflexes. Myoclonus, asterixis, and chorea can be present; tonic-clonic and absence seizures have been described. Hyperglycemia is a particularly common consequence of hypernatremia in children. Severe hypernatremia can also result in rhabdomyolysis. While earlier publications reported that hypocalcemia was associated with hypernatremia, this was not observed in more recent literature. The degree of central nervous system depression appears to correlate with the severity of hypernatremia.

Patients with hepatic encephalopathy are at highest risk for developing cerebral demyelination from iatrogenic hypernatremia due to rapid overcorrection of preexisting hyponatremia.

30.2.4 Treatment

The cornerstone of hypernatremia management is providing adequate free water to correct the serum sodium concentration but doing this at a rate that limits the risk of brain injury. Hypernatremia is frequently accompanied by volume depletion; if hemodynamic instability is present, fluid resuscitation with an isotonic solution should be instituted to establish more normal hemodynamics prior to slowly correcting the free water deficit. Following initial volume expansion, the composition of parenteral fluid therapy largely depends on the etiology of the hypernatremia. Patients with sodium overload or a renal concentrating defect require a more hypotonic fluid than patients with volume depletion and intact renal concentrating ability. Oral hydration should be instituted as soon as it can be safely tolerated. Plasma electrolytes should be checked frequently until adequate correction is achieved.

A simple way of estimating the minimum amount of fluid necessary to correct the serum sodium is by the following equation:

$$\text{Free water deficit}(\text{mL}) = 4\text{mL} \times \text{lean body wt}(\text{kg}) \times [\text{Desired change in serum Na in mEq/L}]$$

Larger amounts of fluid are required depending on the fluid composition. To correct a 3 L free water deficit, approximately 4 L of 0.2% sodium chloride in water or 6 L of 0.45% sodium chloride in water would be required as they contain approximately 75% and 50% free water, respectively. The calculated deficit does not account for insensible losses or ongoing urinary or gastrointestinal losses. Maintenance fluids, which include replacement of urine volume with hypotonic fluids, are given in addition to the deficit replacement. Glucose containing replacement fluids should be limited as they can result in significant hyperglycemia.

The rate of correction of hypernatremia is largely dependent on the severity of the hypernatremia and the etiology. Due to the brain's relative inability to extrude unmeasured organic substances (idiogenic osmoles), rapid correction of hypernatremia can lead to cerebral edema. While there are no definitive

studies that document the optimal rate of correction without developing cerebral edema, empirical data have shown that unless symptoms of hypernatremic encephalopathy are present, a rate of correction not exceeding 1 mEq/h or 15 mEq/24 h is reasonable. In severe hypernatremia (>170 mEq/L), serum sodium should not be corrected to below 150 mEq/L in the first 48–72 h. If the patient is at high risk for developing cerebral edema, such as with head trauma or encephalitis, the rate of correction of hypernatremia should be slower.

Seizures occurring during the correction of hypernatremia are not uncommon in children and may be a sign of cerebral edema. Hypotonic fluid infusion should be ceased, and hypertonic saline should be administered when cerebral edema is suspected during the correction of hypernatremia. The presence of signs of intracranial hypertension, such as headache, hypertension, bradycardia, abnormal respiratory pattern, and coma, warrants rapid treatment including securing the airway, osmolar therapy, and hyperventilation if herniation seems imminent. In symptomatic children, assessment of progressive cerebral edema by computed tomography of the head is indicated. Seizures not associated with concomitant cerebral swelling are usually self-limited and not a sign of long-term neurological sequelae.

Certain forms of therapy for hypernatremia require special mention.

In the setting of hemodynamic compromise, fluid resuscitation with 0.9% sodium chloride should precede the correction of the free water deficit in hypernatremic dehydration.

30.2.5 Central Diabetes Insipidus

Patients with central diabetes insipidus typically have a high urine output with hypotonic urine compared with the serum osmolality and a greater than 50% increase in urine osmolality in response to the first dose of dDAVP.

Central diabetes insipidus (CDI) is an important cause of hypernatremia in the intensive care setting that must be recognized early as it requires specific therapy. CDI results from inadequate arginine vasopressin (AVP) secretion. CDI in the intensive care setting typically presents with abrupt polyuria and free water diuresis. Severe hypernatremia can develop in an individual who has restricted access to fluids and is receiving sodium-containing parenteral fluids. Common causes of CDI in the intensive care setting include traumatic brain injury, brain tumors, pituitary surgery (e.g., postoperative craniopharyngioma resection), central nervous system infections, and cerebral hemorrhages or infarcts. CDI occurs most commonly in the setting of brain death. Because patients with CDI conserve sodium appropriately, they typically do not manifest signs of volume depletion unless the diagnosis is delayed. Polyuria and a urine osmolality that is not maximally concentrated in the presence of hypernatremia suggest a renal concentrating defect. In CDI, the urine osmolality is typically much less than the plasma osmolality. The treatment of CDI includes the correction of free water deficit and the administration of the AVP synthetic analog, desmopressin acetate (dDAVP). Desmopressin can be administered subcutaneously, intranasally, or intravenously. In critically ill patients, edema and peripheral vasoconstriction may preclude effective subcutaneous administration; therefore, intravenous administration of dDAVP or vasopressin may be required. In CDI, there will typically be a greater than 50% increase in urine osmolality in response to dDAVP concomitant with a reduction in urinary output.

30.2.6 Hypernatremia in the Edematous Patient

While hypernatremia is usually associated with volume depletion, some patients in the intensive care setting may have hypernatremia with edema. This typically occurs in patients with either multisystem organ failure or acute renal insufficiency. These patients initially present with a normal serum sodium and become increasingly edematous following the administration of large amounts of volume in the form of saline, colloid, or blood products to restore circula-

tory volume. Iatrogenic hypernatremia then develops if the patient has either urinary or gastrointestinal free water losses in combination with fluid restriction and ongoing saline administration. The free water diuresis is usually due to loop diuretics, renal insufficiency, an osmotic diuresis, or tubular dysfunction from medications. This clinical scenario must be recognized early as the hypernatremia can be prevented if sodium is removed from all continuous infusions. If the patient is receiving multiple medications in IV fluid, the type of fluid used may need to be changed to a low or no sodium formulation, such as D_5W. It may not be possible to correct hypernatremia in the edematous patient with free water alone if there is severe renal insufficiency or marked fluid overload leading to congestive heart failure or pulmonary congestion. In this situation, renal replacement therapy may be required to correct both fluid overload and hypernatremia.

30.3 Hyponatremia

30.3.1 Pathogenesis

Hyponatremia usually signifies impaired free water excretion due to excess AVP production.

Hyponatremia typically develops when a relative excess of free water is accompanied by an underlying condition that impairs the kidney's ability to excrete free water.

There are hemodynamic and non-hemodynamic stimuli for AVP production that place the ICU patient at risk for hyponatremia.

Hyponatremia is defined as a serum sodium <135 mEq/L. The body's primary defense against developing hyponatremia is the kidney's ability to generate dilute urine and excrete free water. Excess ingestion of free water alone is rarely the cause of hyponatremia. However, infants are at increased risk for hyponatremia due to water intoxication as a result of inappropriate administration of free water or overly dilute formula preparation. It is also rare to develop hyponatremia from excess urinary sodium losses in the absence of free water ingestion except for children with cerebral salt wasting, as described later. In order for hyponatremia to develop, it typically requires a relative excess of free water in conjunction with an underlying condition that impairs the kidney's ability to excrete free water (► Box 30.1). Thus, there is a component of impaired water excretion in hyponatremic states. Renal water handling is primarily under the control of AVP, which is produced in the hypothalamus and released from the posterior pituitary. AVP inhibits water diuresis by increasing the permeability to water in the collecting tubule. There are osmotic, hemodynamic, and non-hemodynamic stimuli for AVP release. In most cases of hyponatremia, there is a stimulus for vasopressin production that results in impaired free water excre-

Box 30.1 Disorders with Impaired Renal Water Excretion

1. Effective circulating volume depletion.
   (a) Gastrointestinal losses: Vomiting, diarrhea.
   (b) Skin losses: Cystic fibrosis.
   (c) Renal losses: Salt wasting nephropathy, diuretics, cerebral salt wasting, hypoaldosteronism.
   (d) Edematous states: Heart failure, cirrhosis, nephrosis, hypoalbuminemia.
2. Thiazide diuretics.
3. Renal failure.
   (a) Acute.
   (b) Chronic.
4. Non-hypovolemic states of ADH excess.
   (a) SIADH.
   (b) Cortisol deficiency.
   (c) Hypothyroidism.

Table 30.3 Common causes of SIADH

Central nervous system disorders	Carcinomas
Infection: Meningitis, encephalitis	Bronchogenic carcinomas
Neoplasms	Oat cell of the lung
Vascular abnormalities	Duodenum
Psychosis	Pancreas
Hydrocephalus	Neuroblastoma
Postpituitary surgery	
Head trauma	
Pulmonary disorders	**Medications**
Pneumonia	Vincristine
Tuberculosis	Intravenous Cytoxan
Asthma	Carbamazepine
Positive pressure ventilation	Oxcarbazepine
Pneumothorax	Serotonin reuptake inhibitors

tion. It is important to recognize that the body will attempt to preserve extracellular volume at the expense of the serum sodium; therefore, a hemodynamic stimulus for AVP production overrides the inhibitory effect of hyponatremia. There are numerous stimuli for AVP production (Table 30.3) that make many hospitalized children at risk for hyponatremia due to the syndrome of inappropriate ADH (SIADH).

30.3.2 Diagnosis

Hyperglycemia causes a hyperosmolar hyponatremia due to a translocation of water from the intracellular to the extracellular space. The serum sodium falls by 1.6 mEq/L for every 100 mg/dL rise in blood glucose concentration above normal.

Before embarking on an aggressive therapeutic regimen, it is vital to confirm that hyponatremia is in fact associated with hypoosmolality. Hyponatremia can be associated with either a normal or an elevated serum osmolality (Fig. 30.2). The most common reasons for the latter are hyperglycemia, severe hyperproteinemia, or hyperlipidemia. Hyperglycemia results in hyperosmolality with a translocation of fluid from the intracellular space to the extracellular space, resulting in a 1.6 mEq/L fall in the serum sodium for every 100 mg/dL elevation in the serum glucose concentration above normal. Severe hyperlipidemia, hypercholesterolemia, hyperproteinemia, or radiocontrast and intravenous immunoglobulin infusions can displace plasma water, resulting in a decreased sodium concentration (pseudohyponatremia) with a normal serum osmolality. Serum sodium is currently measured by either direct or indirect-reading ion-selective electrode potentiometry. The direct method will not result in a diagnosis of pseudohyponatremia as it measures the activity of sodium in the aqueous phase of serum only. Conversely, the indirect method can result in pseudohyponatremia as the specimen is diluted with a reagent prior to measurement. The indirect method is currently performed in approximately 60% of chemistry labs in the United States; therefore, clinicians need to be aware of pseudohyponatremia. If hyponatremia is associated with hypoos-

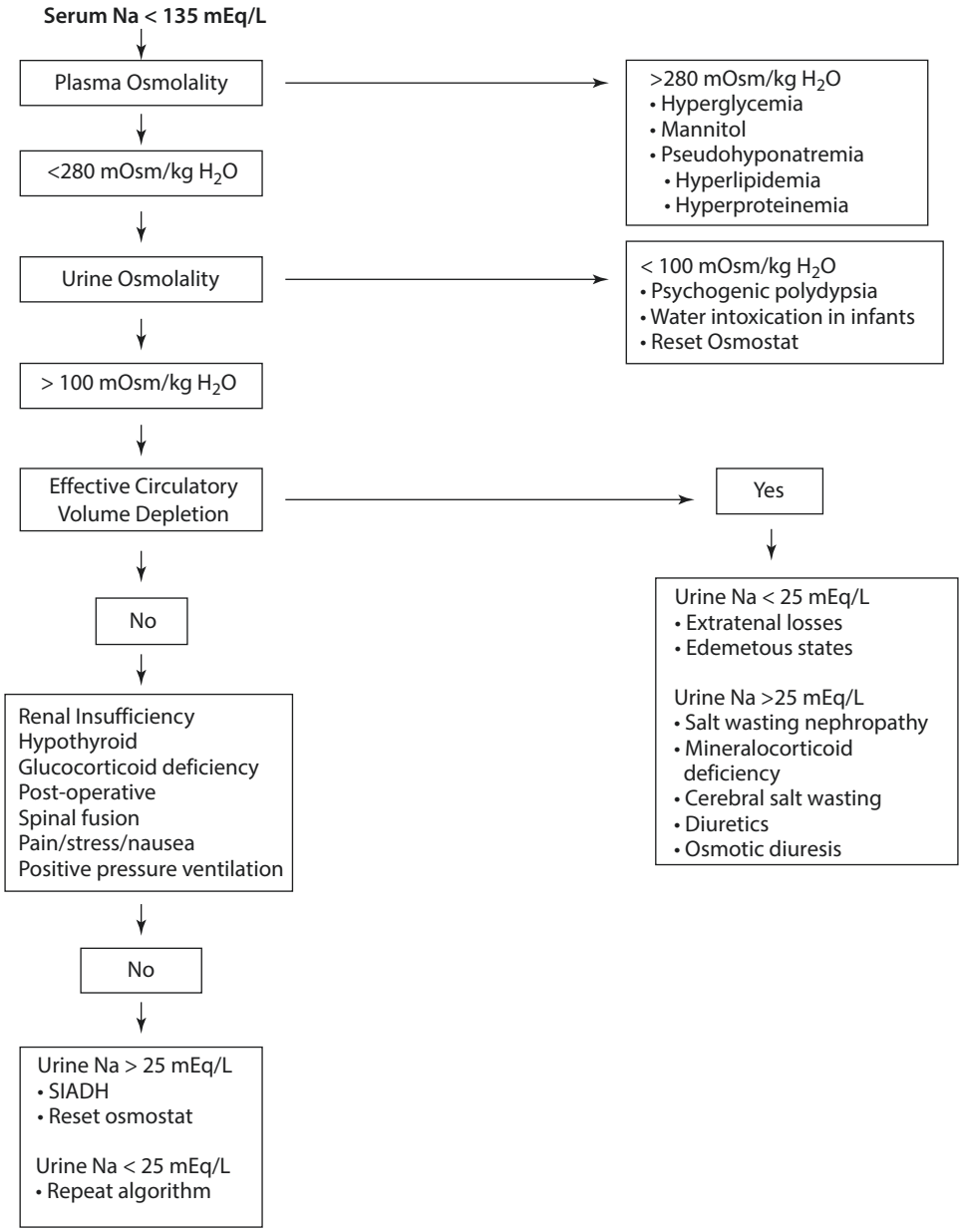

Fig. 30.2 Diagnostic approach to hyponatremia

molality (true hyponatremia), the next step is to measure the urinary osmolality to determine if there is an impaired ability to excrete free water ($Urine_{Osm}$ > 100 mOsm/kg).

The information that is most useful in arriving at a correct diagnosis of hyponatremia is a detailed history of fluid balance, weight changes, medications (especially diuretics), and underlying medical illnesses. Hyponatremia is usually a multifactorial disorder, and a detailed history helps identify sources of salt and water losses, free water ingestion, and underlying illnesses that cause a nonosmotic stimulus for vasopressin production. An assessment of the volume status on physical examination and measuring the urinary electrolytes and osmolality can be extremely helpful, but both can be misleading. In patients in whom hyponatremia is due to salt losses, such as diuretics, signs of volume depletion may be absent on physical examination as the volume defi-

cit may be nearly corrected due to oral intake of hypotonic fluids if the thirst mechanism is intact or in NPO children receiving hypotonic IV fluids.

In general, a urinary sodium concentration less than 25 mEq/L is consistent with effective circulating volume depletion, while a urine sodium greater than 25 mEq/L is consistent with renal tubular dysfunction, use of diuretics, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Numerous factors can affect the urine sodium concentration, making interpretation difficult; therefore, the timing of the urinary measurements in relation to dosages of diuretics, intravenous fluid boluses, or fluid and sodium restriction are also important. In some cases, estimation of intravascular volume status by the measurement of a central venous pressure may be helpful.

Before SIADH can be diagnosed, diseases causing decreased effective circulating volume, renal impairment, adrenal insufficiency, and hypothyroidism must be excluded. Cortisol deficiency in particular should be ruled out as it can be clinically indistinguishable from SIADH and can manifest in times of stress. Glucocorticoid hormones exert an inhibitory effect on AVP synthesis, which is why patients with glucocorticoid deficiency have markedly elevated AVP serum concentrations that are rapidly reversed by physiologic hydrocortisone replacement. A serum cortisol concentration in the normal range does not rule out adrenal insufficiency as the cause of hyponatremia as the appropriate adrenal response to hyponatremia would be to increase cortisol production. An adrenocorticotropic hormone (ACTH) stimulation test should be considered if the cortisol serum concentration is not appropriately elevated in the setting of hyponatremia. Hypothyroidism can also resemble SIADH in infants.

30.3.3 Hospital-Acquired Hyponatremia and its Prevention

Hospital-acquired hyponatremia is of concern in children as the standard of care in pediatrics had been to administer hypotonic maintenance fluids containing 0.2–0.45% sodium chloride. The safety of this approach had never been established. Hospitalized children have numerous nonosmotic stimuli for increased vasopressin production that place them at risk for developing hyponatremia. Critically ill children are at higher risk as most have multiple nonosmotic stimuli for AVP secretion (e.g., pulmonary disorders, mechanical ventilation, intracranial injury). There are over 50 reported cases in the past 10 years of neurologic morbidity and mortality resulting from hospital-acquired hyponatremia in children receiving hypotonic parenteral fluids. Over half of these cases occurred in the postoperative setting in previously healthy children undergoing minor elective surgeries. Hyponatremia is especially dangerous in children with underlying CNS injury such as encephalitis, wherein even mild hyponatremia (sodium >130 mEq/L) may result in cerebral edema and even herniation. In 2018, the American Academy of Pediatrics issued a Clinical Practice Guideline on maintenance intravenous fluids stating that the most important measure to prevent hyponatremia is to avoid using hypotonic fluids in children who have clear risks for nonosmotic AVP secretion and to initially administer isotonic saline (0.9% sodium chloride) unless otherwise clinically indicated. These recommendations were based on over 20 prospective trials in almost 3000 patients demonstrating that isotonic fluids decrease the incidence of hyponatremia three- to sixfold in comparison with hypotonic fluids. The serum sodium should be followed in any patient receiving continuous parenteral fluid and adjustments to the composition of intravenous fluids made accordingly.

Clinical indications to not use 0.9% sodium are primarily in disease states associated with increased free water losses, such as renal concentrating defects, voluminous diarrhea, or severe burns. Furthermore, children with neurosurgical disorders, significant congenital or acquired heart disease, hepatic or renal dysfunction, fluid overload, or edema, children undergoing or who recently received chemotherapy, or children <28 days old or in the NICU may require a different maintenance fluid composition and infusion rate.

The most important factor resulting in hospital-acquired hyponatremia is the administration of hypotonic fluids to patients with compromised ability to excrete free water.

30.3.4 Hyponatremic Encephalopathy

30.3.4.1 Clinical Symptoms

A major consequence of hyponatremia is the influx of water into the intracellular space resulting in cellular swelling, leading to cerebral edema and encephalopathy. The symptoms of hyponatremic encephalopathy can be quite variable, with the only consistent symptoms being headache, nausea, vomiting, emesis, and weakness. As cerebral edema worsens, patients develop behavioral changes, with impaired response to verbal and tactile stimuli. Advanced symptoms are consequences of cerebral herniation, with seizures, respiratory arrest, dilated pupils, and decorticate posturing. Not all patients have the usual progression of symptoms such that advanced symptoms can present with sudden onset.

Headache, nausea, and vomiting are the most consistent symptoms of hyponatremic encephalopathy.

30.3.4.2 Risk Factors for Developing Hyponatremic Encephalopathy

Age

Children under 16 years of age are at increased risk for developing hyponatremic encephalopathy due to their relatively larger brain to intracranial volume ratio as compared to adults. A child's brain reaches adult size by 6 years of age, whereas the skull does not reach adult size until 16 years of age. Consequently, children have less room available in their rigid skulls for brain expansion and are likely to develop brain herniation from hyponatremia at higher serum sodium concentrations than adults. Immediate initiation of appropriate therapy is crucial to prevent significant morbidity.

Children develop hyponatremic encephalopathy at higher serum sodium concentrations than adults as a result of the child's large brain to intracranial volume ratio.

Hypoxia

Hypoxemia is a significant contributor to the development of hyponatremic encephalopathy and long-term neurological sequelae. The combination of systemic hypoxemia and hyponatremia is more deleterious than is either factor alone because hypoxemia impairs the ability of the brain to adapt to hyponatremia. Hyponatremia alone leads to a decrement of cerebral blood flow. Additionally, patients with symptomatic hyponatremia can develop hypoxemia by at least two different mechanisms resulting from cerebral edema: neurogenic pulmonary edema and hypercapnic respiratory failure secondary to obtundation/coma. Respiratory failure can occur suddenly; severe neurologic morbidity is seen in patients with hyponatremia who suffered a respiratory arrest as a feature of their hyponatremic encephalopathy.

Syndrome of Inappropriate Antidiuretic Hormone Production (SIADH)

SIADH is one of the most common causes of hyponatremia in the hospital setting and frequently leads to severe hyponatremia (plasma Na <120 mEq/L). It is caused by elevated ADH secretion in the absence of an osmotic or hypovolemic stimulus. SIADH can occur due to a variety of illnesses but most often occurs due to central nervous system disorders, pulmonary disorders, and

medications (Table 30.3). Among the latter, the chemotherapeutic drugs vincristine and Cytoxan and the antiepileptic drug, carbamazepine, are especially common causes. SIADH is essentially a diagnosis of exclusion (Fig. 30.2). Before SIADH can be diagnosed, diseases causing decreased effective circulating volume, renal impairment, adrenal insufficiency, and hypothyroidism must be excluded. The hallmarks of SIADH are mild volume expansion with low to normal plasma concentrations of creatinine, urea, uric acid, and potassium; impaired free water excretion with normal sodium excretion which reflects sodium intake; and hyponatremia that is relatively unresponsive to sodium administration in the absence of fluid restriction. The biochemical parameters most suggestive of SIADH in adults are a spot urine sodium concentration > 30 mEq/L, a fractional excretion of sodium >0.5%, fractional excretion of urea >55%, fractional excretion of urate (FEUrate) >11%, and plasma uric acid <4 mg/dl. The specificity and sensitivity of these biomarkers have not been evaluated in children.

SIADH is usually of short duration and resolves with treatment of the underlying disorder and discontinuation of the offending medication. Fluid restriction is the cornerstone therapy of SIADH. However, fluid restriction results in slow correction of hyponatremia and is frequently impractical in infants who receive most of their nutrition as liquids. Intravenous fluids should be of tonicity greater than or equal to normal saline. Should this not be sufficient to correct the plasma sodium, 3% sodium chloride may be given as needed. If a more rapid correction of hyponatremia is needed, the addition of a loop diuretic in combination with hypertonic saline is useful.

For children with chronic asymptomatic hyponatremia from SIADH that does not respond to fluid restriction, the next step is to increase the oral sodium intake or give oral urea in order to increase the renal solute load, thereby inducing an osmotic diuresis. Oral urea has been successful in treating chronic hyponatremia in both children and adults who did not respond to conservative measures. A once-daily dose of 15–30 g of urea in an adult appears to be effective and well tolerated. A commercially available lemon-flavored urea powder drink (Ure-Na by Nephcentric LLC) is now available in the United States.

SIADH occurs when normal extracellular volume is maintained at the expense of serum sodium.

Vasopressin-2 antagonists (vaptans) represent a relatively new class of medication for the management of SIADH. These agents selectively antagonize the antidiuretic effect of AVP and result in a urinary free water diuresis (aquaresis) without increasing loss of electrolytes. Vaptans produce an aquaresis within 1–2 h of administration which abates within 12–24 h. When used to treat hyponatremia, vaptans result in an approximately 5–7 mEq/L increase in serum sodium within the first 24 h of administration, but the effect is highly variable. The most common side effects of vaptans are increased thirst, polyuria, and dry mouth. There are currently two vaptans that are FDA approved in the United States: tolvaptan, which is available in an oral formulation, and conivaptan, which is available in an intravenous preparation. There are safety concerns with vaptans as they have been associated with alanine aminotransferase elevation and severe hepatotoxicity with long-term use, and serious overcorrection of hyponatremia has been reported. Overcorrection is of particular concern in neurologically impaired or critically ill children with restricted access to water. These agents are inhibitors of cytochrome P450 and should not be used in conjunction with other drugs known to be metabolized by this pathway. At the present time, vaptans cannot be recommended as a first-line agent in the management of SIADH as they are expensive, are not always necessary, and present safety concerns. Vaptans do appear to be a suitable second-line agent for short-term use in patients with SIAD after conservative measures have failed.

Cerebral Salt Wasting (Also See ▶ Chap. 43)

In the setting of CNS injury or following a neurosurgical procedure, hyponatremia is usually attributed to SIADH, a condition whose hallmark is euvolemia to mild hypervolemia, with the cornerstone of management being fluid restriction. More recently, it has become apparent that an increasing number of neurosurgical patients with hyponatremia have a distinct clinical entity called cerebral salt wasting (CSW), a condition whose hallmark is renal sodium loss leading to extracellular volume depletion. The cornerstone of management is volume expansion and salt supplementation. Because these two diseases have many clinical similarities, it can be difficult to confirm a diagnosis of CSW, but it is essential to distinguish between these two conditions as their management is completely different, and fluid restriction would be harmful in the presence of CSW.

The pathogenesis of CSW is not completely understood, but it appears to be due to the release of natriuretic peptides, such as atrial natriuretic peptide, brain natriuretic peptide, and C-type natriuretic peptide. These peptides cause a natriuresis via a complex mechanism of (1) hemodynamic effects leading to an increased GFR, (2) inhibition of the renin-angiotensin system, and (3) inhibition of the secretion and action of AVP. This complex mechanism can lead to laboratory values that are indistinguishable from SIADH with a low uric acid, plasma renin, aldosterone, and vasopressin levels despite volume depletion. The key distinguishing feature between CSW and SIADH is extracellular volume depletion. Careful documentation of trends in urinary output and central venous pressure is particularly useful. An algorithm using changes in the fraction excretion of urate (FEUrate) has recently been validated for distinguishing SIADH from CSW. While both SIADH and CSW are associated with hypouricemia and an elevated FEUrate of >11%, the FEUrate normalized following the correction of hyponatremia in SIADH, whereas the FEUrate remains persistently elevated following the correction of serum sodium in CSW.

From a practical standpoint, the administration of normal saline should be an adequate prophylaxis against developing clinically significant hyponatremia, <130 mEq/L, in SIADH. If clinically significant hyponatremia develops in a patient with a CNS disorder receiving only normal saline, then the diagnosis of CSW should be strongly considered. If there are no signs of extracellular volume depletion, then a brief period of fluid restriction can be tried. If there are signs of volume depletion or a lack of response to fluid restriction with a further fall in the serum sodium concentration, then the patient should be managed as CSW. Patients with CSW should be volume expanded with normal saline, followed by sufficient quantities of normal saline and 3% NaCl, to maintain fluid balance and normal serum sodium. The administration of fludrocortisone may be beneficial as aldosterone production is relatively decreased in CSW.

30.3.4.3 Treatment of Hyponatremic Encephalopathy

There are two aspects of the treatment of hyponatremic encephalopathy generally accepted by experts in the field: (1) treatment should be based on the neurological involvement and not the absolute serum sodium, and (2) hypertonic saline is not indicated in the asymptomatic patient who is neurologically intact, regardless of the serum sodium concentration. In general, rapid correction with hypertonic saline is unnecessary and potentially harmful if there are no neurological symptoms. Conversely, symptomatic hyponatremia is a medical emergency. Treatment of hyponatremic encephalopathy should precede any neuroimaging studies to confirm cerebral edema and should occur in a monitored setting where the airway can be secured and serum sodium level measured frequently. Fluid restriction alone has no place in the treatment of

symptomatic hyponatremia. If symptomatic hyponatremia is recognized and treated promptly, prior to the development of a hypoxic event, the neurological outcome is good.

Patients with symptomatic hyponatremia should be treated with hypertonic saline (3% sodium chloride); children without symptoms should not receive hypertonic saline.

Patients with symptomatic hyponatremia need aggressive management with 3% NaCl (Na = 513 mEq/L). In general, 1 mL/kg of 3% NaCl will increase the serum sodium level by about 1 mEq/L. Children with severe symptoms such as seizures, respiratory arrest, or neurogenic pulmonary edema should receive 2 mL/kg of 3% NaCl, with a maximum of 150 mL, as a bolus over 10 min to rapidly reverse brain edema. This dose might need to be repeated once or twice until symptoms subside, with the remainder of therapy delivered via continuous infusion. Patients with less severe symptoms, such as headache, nausea, vomiting, or lethargy, can be treated via an infusion pump to achieve a sodium correction of 4–8 mEq/L in the first 4 h. To prevent complications arising from excessive therapy, 3% NaCl should be discontinued when symptoms subside. The rate of Na correction should not exceed 20 mEq/L in the first 48 h, and correction should be to mildly hyponatremic values, avoiding normalization of serum sodium or hypernatremia in the first 48 h. A continuous infusion of 3% NaCl at a rate of 1–2 mL/kg/h administered over 4 h is usually sufficient to reverse symptoms.

Cerebral Demyelination Complicating the Correction of Hyponatremia

Cerebral demyelination is a rare complication associated with symptomatic hyponatremia. Animal data has shown that correction of hyponatremia by greater than 20–25 mEq/L over 24 hours can result in cerebral demyelination. These observations have resulted in a mistaken belief that a rapid rate of correction alone is likely to result in cerebral demyelination. More recent data demonstrated that the development of cerebral demyelinating lesions is more likely due to comorbid factors such as severe liver disease, hypoxemia, hypokalemia, or chronic thiazide diuretic use rather than rate of correction alone. Cerebral demyelination following the correction of hyponatremia has primarily been described in patients with chronic hyponatremia (>48 h) and is an extremely unusual occurrence in acute symptomatic hyponatremia. Also, cerebral demyelination appears to be a less common occurrence in children than in adults.

When symptomatic cerebral demyelination follows the correction of hyponatremia, it typically follows a biphasic pattern. There is initial clinical improvement of the hyponatremic encephalopathy associated with correction of the serum sodium, which is followed by neurological deterioration 2–7 days later. Cerebral demyelination can be both pontine and extrapontine. Classic features of pontine demyelination include mutism, dysarthria, spastic quadriplegia, pseudobulbar palsy, a pseudocoma with a "locked-in stare," and ataxia. The clinical features of extrapontine lesions are more varied, including behavior changes and movement disorders. Radiographic features of cerebral demyelination typically lag behind the clinical symptoms. Cerebral demyelination is best diagnosed by MRI approximately 14 days following hyponatremia correction. The classic MRI findings are symmetrical hypointense lesions on T1-weighted images and hyperintense lesions on T2-weighted images. Some data suggest that cerebral demyelination can be detected earlier on MRI with diffusion-weighted imaging.

The outcome of cerebral demyelination is not as severe as was previously believed. Cerebral demyelination has been noted as an incidental finding on neuroimaging and at autopsy in patients with chronic illnesses. In most reported cases of cerebral demyelination attributed to dysnatremias, long-term follow-up demonstrated improvement in neurological symptoms and regres-

sion of radiographic findings. Thus, the primary cause of brain damage in patients with hyponatremia is not cerebral demyelination but results from cerebral edema and herniation. Most brain damage occurs in untreated patients and is not a consequence of therapy.

Patients with hyponatremia due to water intoxication, diarrheal dehydration, thiazide diuretics, or dDAVP are at high risk for overcorrection of hyponatremia and require extreme care and monitoring. In these illnesses, once volume depletion is corrected or when the offending medication is discontinued, there often is a rapid reversal of the urine osmolality from concentrated to dilute, resulting in a free water diuresis with potentially rapid correction of hyponatremia if saline-containing fluids are continually administered. The serum sodium can be therapeutically relowered in patient with overcorrection of severe chronic hyponatremia having other risk factors for demyelination by using a combination of dDAVP and 5% dextrose in water.

The major risk factors for developing cerebral demyelination following the correction of hyponatremia are (1) overcorrection of chronic hyponatremia, (2) inadvertent hypernatremia, (3) hypoxia, and (4) preexisting liver disease.

The primary cause of brain injury in children with hyponatremia is not cerebral demyelination but results from cerebral edema and herniation.

30.3.5 Hyponatremia in Edematous States

Edema is a common clinical finding in ICU patients and can occur in a variety of disease states including hypernatremia as previously described. Edema is defined as palpable swelling due to the expansion of the interstitial space. The common conditions that lead to edema are congestive heart failure, hepatic cirrhosis, nephrotic syndrome, sepsis, and acute kidney injury. The mechanism of edema formation and its treatment is different in each of these conditions, but all have in common an impaired ability to excrete free water, which makes hyponatremia a common associated complication. These patients rarely have symptomatic hyponatremia, but even mild hyponatremia is a major comorbidity factor which should be prevented and treated.

30.3.5.1 Pathophysiology

The development of edema requires an alteration in one or more of the Starling forces. Starling's law depicts the relationship between net filtration from the vascular space based on alterations in hydrostatic pressure, plasma oncotic pressure, and capillary permeability.

30.3.5.2 Increased Capillary Hydraulic Pressure

The most common causes of edema due to increased capillary hydraulic pressure are congestive heart failure and cirrhosis. In congestive heart failure, there is decreased cardiac output impairing renal perfusion and thus urine output leading to fluid retention with increased ventricular end-diastolic pressures. This results in a compensatory response including (a) increased sympathetic tone leading to peripheral and renal vasoconstriction, (b) increased activity of the renin-angiotensin-aldosterone system which increases renal sodium retention, and (c) increased AVP production which results in water retention. These factors expand the vascular space and retain water leading to hyponatremia. As venous pressures increase, capillary hydrostatic pressure increases leading to interstitial expansion and edema.

The primary event leading to edema in cirrhosis is increased hepatic resistance to portal flow which results in increased capillary hydrostatic pressure leading to bowel edema. As liver injury progresses, there is inappropriate arterial vasodilation leading to low blood pressure and intravascular volume relative to the capacity of the vascular space, which activates the renin-angiotensin-aldosterone system and increases vasopressin release leading to fluid and sodium retention (similar to the neurohumoral response seen in heart failure patients).

In addition, as ascites progresses, intra-abdominal pressure increases, leading to compression of the inferior vena cava which increases the likelihood for lower extremity edema.

30.3.5.3 Decreased Plasma Oncotic Pressure

Hypoalbuminemia due to renal loss is a significant, but not the only, contributing factor to edema formation in children with nephrotic syndrome. In severe hypoalbuminemia, the low capillary oncotic pressure favors fluid movement into the interstitial space. In nephrotic syndrome, the renal disease itself can lead to sodium retention, which may be the main contributing factor to edema formation. In liver disease, decreased production of proteins such as albumin leads to a fall in oncotic pressure.

30.3.5.4 Increased Capillary Permeability

Increased capillary permeability due to conditions such as burns, trauma, or sepsis can lead to edema. Edema formation is due to both fluid movement across blood vessels and to decreased capillary oncotic pressure from albumin leaking into the interstitial space.

30.3.5.5 Treatment of Hyponatremia in Edema-Forming States

Hyponatremia in edema-forming states can be difficult to treat. The cornerstone of management is treating the underlying condition, which differs by etiology. As a general rule, patients with hyponatremia and edema should be fluid restricted, and hypotonic fluids should not be given. Thiazide diuretics are a major contributing factor to the development of hyponatremia in edematous states, and their use should be limited if significant hyponatremia is present. Thiazide diuretics act at the distal convoluted tubule causing sodium and potassium loss without impairing urinary concentration. Loop diuretics are the preferred agents in the hyponatremic patient as they impair urinary concentration and lead to urinary free water loss. The administration of 25% albumin in the treatment of edema is controversial, but in all likelihood, it is beneficial when the serum albumin is <2 g/dL and may facilitate the correction of hyponatremia. Vasopressin-2 antagonists have been used in adults to correct edematous hyponatremia.

30.4 Hypocalcemia

30.4.1 Calcium Homeostasis

Approximately 1% of total body calcium resides in the extracellular volume, with the remaining 99% residing in the bone as calcium phosphate apatite. Extracellular calcium occurs in three fractions: ~40% protein bound, ~50% ionized, and ~10% in a chelated form. The majority of calcium that is protein bound is bound to albumin. Ionized (i.e., free) calcium is the biologically important fraction. A change in serum albumin concentration or pH can cause the total serum calcium and ionized calcium to fluctuate independently of each other. The total serum calcium falls by 0.8 mg/dL (0.2 mmol/L) for every 1 g/dL decrease in serum albumin concentration without affecting the ionized calcium concentration. Ionized calcium concentration rises with acidemia and falls with alkalemia (an increase in pH of 0.1 unit leads to a fall in ionized calcium by 0.16 mg/dL) without affecting the total serum calcium. These changes are mediated by proton competition for the calcium-albumin binding sites. For these reasons, ionized calcium must be measured to evaluate hypocal-

cemia as the total serum calcium does not adequately reflect the physiologically relevant ionized calcium.

The serum calcium is tightly regulated by an interplay of the calcium sensing receptor, parathyroid hormone (PTH), and 1,25 dihydroxyvitamin D_3 ($1,25(OH)D_3$). The calcium sensing receptor is primarily located on the cell surface of the parathyroid gland, where it responds to low ionized calcium by causing a prompt release of PTH; the latter results in a rapid release of calcium from the bone, increased renal tubular calcium reabsorption and phosphorous excretion, and the 1-hydroxylation of $25(OH)D_3$. 1,25 dihydroxyvitamin D_3 increases intestinal calcium absorption and bone resorption, further increasing serum calcium.

The total serum calcium falls by 0.8 mg/dL (0.2 mmol/L) for every 1 g/dL decrease in the serum albumin concentration.

Ionized calcium is the biologically important fraction of serum calcium and must be measured to evaluate and monitor hypocalcemia.

30.4.2 Etiology of Hypocalcemia (Table 30.4)

Severe hypocalcemia is a medical emergency. Symptoms of hypocalcemia can include seizures, tetany, muscle cramps, laryngospasm, neuromuscular irritability, and paresthesias. It can also contribute to hypotension in the critically ill child. The cardiac manifestations of hypocalcemia include a prolonged Q-Tc interval as hypocalcemia prolongs myocardial repolarization. Untreated hypocalcemia may lead to ventricular fibrillation or heart block. There are numerous causes of hypocalcemia in children; many of them are quite rare and are not likely to be encountered in the critical care setting. Causes of symptomatic hypocalcemia that are sufficiently common to be encountered in the critical care setting are discussed.

Neonatal hypocalcemia is relatively common in the intensive care unit. Early neonatal hypocalcemia occurring within the first 4 days of birth represents an exaggerated normal fall in serum calcium due to insufficient PTH release from immature parathyroid glands. This is most commonly seen in premature and low-birth-weight infants, infants of diabetic mothers, and with perinatal stress or asphyxia. Late neonatal hypocalcemia occurs between days 5 and 10 of life and is often due to transient PTH resistance. This can occur in conjunction with vitamin D deficiency or excess dietary phosphorous.

Hypoparathyroidism in children most often results from agenesis or dysgenesis of the parathyroid gland. The biochemical features at presentation include a low serum calcium, elevated serum phosphorus, and decreased alkaline phosphatase. The most common cause of hypoparathyroidism is the DiGeorge anomaly and velocardiofacial syndromes, where there is maldevelopment of the third and fourth branchial pouches. The DiGeorge anomaly is most often associated with 22q11 deletion and less often a 10p13 deletion. Hypocalcemia in the setting of congenital heart disease is due to DiGeorge syndrome until proven otherwise. Up to 85% of infants with conotruncal abnormalities have the 22q11 deletion. DiGeorge syndrome has also been documented in nonconotruncal congenital heart disease. Treatment consists of calcitriol and calcium supplements. Treatment should aim to keep the serum calcium low normal as hypercalciuria can develop which can lead to kidney stones or renal insufficiency.

Vitamin D deficiency is not uncommon in patients living in poverty, on very restrictive vegetarian diets, or due to malabsorption states such as intestinal lymphangiectasia. Biochemical features at presentation include a low serum calcium and phosphorous, elevated alkaline phosphatase and PTH, and decreased $25(OH)D_3$. These children typically present between 4 months and 3 years of age with the findings of rickets, delayed linear growth, osteopenia, widening of the epiphyses, rachitic rosary, frontal bossing, leg bowing, and craniotabes. Therapy consists of vitamin D supplementation with ergocalciferol, but oral calcium may be needed until serum calcium normalizes.

Table 30.4 Etiology of hypocalcemia and treatment

Etiology	PTH	Treatment
Neonatal hypocalcemia		Intravenous calcium gluconate.
Early (days 1–4).	↓	
Infant of a diabetic mother		
Prematurity		
Perinatal asphyxia		
Late onset (days 5–10).	↑	
Dietary phosphate load		
Vitamin D deficiency		
Vitamin D deficiency	↑	Ergocalciferol (vitamin D_2).
Malabsorption.		Oral calcium supplements.
Nutritional.		
Hypoparathyroidism	↓	Calcitriol (1,25 dihydroxycholecalciferol).
DiGeorge anomaly (22q11 deletion or 10p13).		Oral calcium supplements.
CHARGE syndrome.		
Autosomal-dominant and autosomal-recessive hypoparathyroidism.		
HDR syndrome (hypoparathyroidism, deafness, renal dysplasia).		
Pseudohypoparathyroidism (type I and II)	↑	Calcitriol.
Impaired vitamin D metabolism	↑	Calcitriol.
Vitamin D-dependent rickets type I (1α-hydroxylase deficiency).		
Vitamin D-dependent rickets type II (end-organ resistance to calcitriol).		
Calcium sensing receptor defect	↓↔	No treatment unless symptomatic.
Cinacalcet (calcimimetic)	↑↔	Discontinue medication.
Calcium deficiency	↑	Oral calcium supplements.
Magnesium deficiency	↕	Magnesium supplements.
Hyperphosphatemia	↑	Phosphorous binders.
		Dialysis.
Renal failure	↑	Calcitriol.
		Calcium supplements.
Disease specific	↕	Phosphorous binders.
Sepsis.		
Acute pancreatitis.		
Rhabdomyolysis.		

Symptomatic hypocalcemia can be the first presenting sign of advanced renal insufficiency. This results from (1) decreased renal production of 1,25(OH) D_3, which reduces intestinal absorption of calcium, and (2) severe hyperphosphatemia, which decreases the serum calcium by causing calcium and phosphorous to precipitate. The administration of bicarbonate to treat acidosis in a patient with renal failure can also cause symptomatic hypocalcemia. The acidosis that is often seen in acute or chronic renal insufficiency raises the ionized calcium; an acute rise in pH following bolus bicarbonate administration causes the ionized calcium concentration to fall. Acidosis should not be treated with bicarbonate in patients with acidosis until the serum calcium is normalized.

The administration of bicarbonate to treat acidosis in patients with renal insufficiency can cause acute symptomatic hypocalcemia.

30.4.3 Hypocalcemia in the Critical Care Setting

Hypocalcemia is common in the critical care setting, occurring in 20–50% of patients, and is associated with increased mortality. The reasons for this are not fully understood, but the incidence appears to increase with disease severity, occurring in as many as 80% of patients with sepsis. Possible reasons for hypocalcemia include a disturbance in the PTH-vitamin D response pathway, with either inappropriate PTH release or resistance to and impaired vitamin D metabolism. Increased vascular permeability seen in sepsis can lead to calcium leaving the vascular space more rapidly than it can be repleted. Calcium can also be chelated by devitalized tissue, citrate in the form of blood products, lipids from parenteral nutrition, and elevated phosphorus levels from renal failure. Hypomagnesemia can also be a contributing factor as magnesium is a key cofactor for appropriate PTH release in response to hypocalcemia.

Magnesium is an essential cofactor for PTH function.

It is not clear that treating hypocalcemia without symptoms in the critically ill patient is beneficial. Some studies report that treating hypocalcemia has beneficial hemodynamic effects, while some animal studies observed increased mortality. In theory, calcium administration could be potentially harmful by increasing intracellular calcium which contributes to cell death. Reasonable indications for correcting hypocalcemia in the critical care setting include symptoms of hypocalcemia such as ECG changes and hemodynamic instability. Infants should also have hypocalcemia aggressively corrected especially in the setting of congenital heart disease. The neonatal myocardium is composed of poorly organized myocytes and a functionally immature sarcoplasmic reticulum that cannot provide sufficient cytosolic calcium for excitation-contraction coupling; hence, the immature myocardium has a greater reliance on extracellular calcium entering the cytoplasm via ion channels. Hypocalcemia should be corrected in all children requiring inotropic or vasopressor support, though recommended targets for ionized calcium levels vary from slightly below the lower limit of normal to low normal.

The value of treating asymptomatic ionized hypocalcemia in critically ill children is unclear. Hypocalcemia should be treated in children on vasoactive drug support, and neonates depend on adequate extracellular calcium concentrations to maintain normal cardiac pumping function.

30.4.4 Acute Management of Hypocalcemia

The treatment of choice for symptomatic hypocalcemia is the administration of 10% calcium gluconate. Calcium gluconate is preferred over calcium chloride as it has less potential for caustic injury when administered peripherally and is safer for prolonged infusions. Further, the chloride load associated with prolonged calcium chloride infusion can be considerable. In emergency situations, calcium can be administered over minutes, but in general, it is given as a slow infusion over 2–4 h. Rapid calcium boluses cause transient marked hypercalcemia with return to baseline level within minutes; thus, continuous infusions are more effective at managing goal-directed calcium levels. Bolus calcium

has been shown to increase blood pressure in adult cardiac patients by virtue of increased systemic vascular resistance at the expense of reduced cardiac output. Patients receiving calcium infusions should have ionized calcium levels monitored frequently. Calcium boluses and infusions should only be administered through central venous catheters (with the exception of life-threatening emergencies) to prevent destructive and disfiguring tissue injuries from the extravasation of the calcium solutions. Hypomagnesemia, if present, should also be corrected with magnesium sulfate as magnesium is an essential cofactor for calcium homeostasis. If acute hypocalcemia must be corrected by the oral route, calcium glubionate should be used as it has the best absorption.

30.5 Hypokalemia

30.5.1 Potassium Homeostasis

Potassium is the most abundant cation in the body; 98% of potassium resides in the intracellular space, and 2% is extracellular. It is the ratio of intracellular to extracellular potassium concentration that determines the resting membrane potential of excitable tissue; therefore, the body must maintain the extracellular potassium concentration in a fairly narrow range of 3.5–5.5 mEq/L to prevent neurological and cardiac conduction disturbances. Potassium can be consumed in large quantities in the diet and is absorbed rapidly in the gastrointestinal tract. Serum potassium is acutely regulated by a transcellular shift of potassium from the extracellular to intracellular compartment by the effect of insulin or stimulation of β_2-adrenoceptors. The long-term regulation of potassium is via urinary excretion which is primarily regulated by aldosterone. The serum potassium does not reflect the total body potassium content as disorders in serum potassium may be due to acute intracellular shift or more chronic potassium depletion or overload. Chronic perturbations in serum potassium are better tolerated than acute changes as the gradient in intracellular to extracellular potassium will be less severe. Chronic hyperkalemia generally reflects a disorder in renal function or decreased mineralocorticoid activity, and chronic hypokalemia represents total body potassium depletion.

Since potassium is measured in either the serum or whole blood, the normal ranges for potassium are different. When blood clots, platelets release their intracellular contents, which includes potassium, so that serum potassium is typically 0.3–0.5 mEq/L higher than whole blood or plasma potassium concentration. In thrombocytopenic patients, the difference is smaller, whereas in patients with high platelet counts, the difference in potassium concentration will be larger.

30.5.2 Clinical Effects of Hypokalemia

Mild hypokalemia can cause serious arrhythmia in the presence of underlying cardiac disease or digoxin use.

Acute serum/plasma potassium concentration changes do not accurately represent total body potassium stores.

Hypokalemia, defined as serum potassium <3.6 mEq/L, is one of the most common electrolyte abnormalities occurring in the critical care setting. Mild hypokalemia, potassium 3–3.5 mEq/L, is usually asymptomatic, and even levels of 2.5–3 mEq/L are often well tolerated in children in the absence of cardiac disease as it does not cause significant arrhythmias. With underlying cardiac disease or digoxin use, even mild hypokalemia can contribute to arrhythmias. In adults, serum potassium <3.0 mEq/L are reported to cause weakness, myopathy, constipation, and intestinal ileus, while serum potassium less than 2.5 mEq/L can cause rhabdomyolysis and ascending paralysis. These symptoms are rarely observed in children even in the critical care setting. When

hypokalemia develops, the underlying cause should be addressed and corrected as hypokalemia is associated with increased morbidity and mortality in both children and adults.

30.5.3 Causes of Hypokalemia in the Critical Care Settings (▸ Box 30.2)

The most common cause of potassium depletion in the critical care setting is from the use of loop or thiazide diuretics, which increase sodium delivery to the collecting duct. This leads to maximal sodium reabsorption in these segments and facilitates potassium excretion through sodium-potassium exchange. Chronic diuretic use may be associated with effective circulating volume depletion, which further stimulates the renin-angiotensin-aldosterone pathway, increasing urinary potassium losses. Hypochloremic metabolic alkalosis, which is a frequent complication of diuretics, contributes to hypokalemia by impairing chloride-linked sodium reabsorption, thereby increasing distal tubule sodium reabsorption in exchange for potassium excretion. Hypomagnesemia, which is a common complication of diuretic therapy, promotes urinary potassium losses by unknown mechanisms. The combination of loop plus thiazide diuretics can lead to significant hypokalemia.

Other disorders leading to hypokalemia are conditions which lead to gastrointestinal losses, transcellular shifts in potassium, or mineralocorticoid excess. Potassium is primarily excreted in the stool by the colonic epithelium;

Box 30.2 Causes of Hypokalemia

1. Inadequate intake.
2. Urinary losses.
   - (a) Diuretics.
   - (b) Salt wasting nephropathy.
     - (i) Fanconi syndrome.
   - (c) Osmotic diuresis.
     - (i) Uncontrolled diabetes.
   - (d) Transport disorder.
     - (i) Bartter's and Gitelman's syndromes.
   - (e) Mineralocorticoid excess.
   - (f) Magnesium depletion.
     - (i) Amphotericin B.
   - (g) Alkalosis.
   - (h) Non-reabsorbable anions (penicillin).
3. Extrarenal losses.
   - (a) Vomiting.
   - (b) Diarrhea.
   - (c) Malabsorption.
   - (d) Tumors.
   - (e) Dialysis.
4. Transcellular shifts.
   - (a) β_2-adrenergic agents,
   - (b) Insulin.
   - (c) Theophylline.
   - (d) Hyperthyroidism.
   - (e) Hypokalemic periodic paralysis.
   - (f) Barium poisoning.

therefore, any process that results in diarrhea can cause large potassium losses. Intestinal losses from an ileostomy or upper gastrointestinal losses from vomiting or nasogastric drainage do not contain significant amounts of potassium. Hypochloremic alkalosis induced by emesis can cause hypokalemia by increasing urinary potassium losses as the kidney attempts to maintain protons. β_2-adrenergics, theophylline, and insulin can cause hypokalemia by causing a transcellular shift in potassium. There are numerous medical conditions associated with increased mineralocorticoid production or activity that can cause hypokalemia, especially in conjunction with diuretics.

30.5.4 Treatment of Hypokalemia

Aggressive parenteral potassium is not indicated unless there are cardiac arrhythmias, severe myopathies, or paralysis.

The treatment of hypokalemia is controversial as excess potassium supplementation, especially via the intravenous route, can cause dangerous hyperkalemia. Hypokalemia is generally asymptomatic, and therapy should aim for a slow correction over a period of days, preferably by the enteral route as potassium chloride in two to three divided doses. In cases of cardiac arrhythmias, severe myopathies, paralysis, or severe hypokalemia (<2 mEq/L), aggressive intravenous administration of potassium is indicated. Potassium should be given as potassium chloride as there is generally an accompanying chloride deficit. Potassium administration should occur at a rate of 0.25–0.5 mEq/kg/h. Symptomatic hypokalemia can be corrected at a maximal rate of 1 mEq/kg/h with a maximum dose of 20 mEq. Many PICUs routinely administer 0.5–1 mEq/kg over 1 h (maximum 20 mEq) without complications as long as strict adherence to administration policy is observed. Neither repeated bolus doses of potassium nor a continuous parenteral fluid containing potassium at a concentration greater than 60 mEq/L should be administered through a peripheral intravenous line as this can sclerose the vein, and potassium infiltration can cause tissue necrosis. Magnesium depletion should be corrected as hypomagnesemia promotes urinary potassium losses. Potassium-sparing diuretics can be helpful to curtail urinary potassium losses.

30.6 Hyperkalemia

30.6.1 Patients at Risk for Hyperkalemia (▶ Box 30.3)

Hyperkalemia is defined as serum potassium greater than 6 mEq/L in newborns and greater than 5 mEq/L in infants and children. Hyperkalemia can develop as a result of either excess potassium intake, decreased potassium excretion, or a transcellular shift of potassium from the intracellular to extracellular space. There are usually multiple factors contributing to hyperkalemia; therefore, a detailed evaluation of potassium intake, renal function, and medication history is mandatory.

Patients with chronic renal insufficiency are able to maintain near normal serum potassium levels unless GFR is less than 10% of normal.

A common setting for serious hyperkalemia in children is oliguric acute kidney injury due to renal ischemia, acute glomerulonephritis, hemolytic uremic syndrome, multiple organ failure, or acute urinary tract obstruction. Patients with chronic renal insufficiency are usually able to maintain near normal potassium until the glomerular filtration rate declines to less than 10% of normal. When a patient with chronic renal insufficiency has serious hyperkalemia, there is usually a secondary cause such as an acute increase in potassium intake or a medication, such as an ACE inhibitor, calcineurin inhibitor (e.g., tacrolimus, cyclosporine), potassium-sparing diuretic, or NSAID, which is impairing the normal renal compensatory response to hyperkalemia. Mineralocorticoid deficiency or resistance can also result in hyperkalemia and should be suspected in any patient with normal renal function and sustained

hyperkalemia. Severe hyperkalemia can develop in infants with pyelonephritis due to a transient pseudohypoaldosteronism. Massive tissue breakdown from rhabdomyolysis or tumor lysis syndrome can also result in serious hyperkalemia. A hyperchloremic metabolic acidosis is the most common cause of hyperkalemia resulting from a transcellular shift in potassium in children. Serum potassium rises on average 0.6 mEq/L (0.24–1.7 mEq/L) for every 0.1 unit fall in pH. Diabetics can also develop hyperkalemia from cellular shift and impaired potassium entry into the cell secondary to insulin deficiency or resistance.

Box 30.3 Causes of Hyperkalemia

1. Factitious.
   (a) Hemolysis.
   (b) Thrombocytosis (platelets > 1,000,000/mm^3).
   (c) Leukocytosis (white blood cell count > 100,000/mm^3).
   (d) Repeated fist clenching with tourniquet in place.
2. Impaired potassium excretion.
   (a) Renal insufficiency or failure.
   (b) Mineralocorticoid deficiency.
      (i) Hereditary enzyme deficiencies.
      (ii) Addison's disease.
      (iii) Hyporeninemic hypoaldosteronism (type 4 renal tubular acidosis).
      (iv) Heparin-induced inhibition of aldosterone synthesis.
   (c) Pseudohypoaldosteronism.
      (i) Hereditary.
      (ii) Pyelonephritis.
3. Medications.
   (a) Potassium-sparing diuretics.
   (b) ACE inhibitors.
   (c) Angiotensin receptor blockers.
   (d) NSAIDs.
   (e) Cyclosporine/tacrolimus.
   (f) Pentamidine.
4. Impaired potassium entry into cells.
   (a) Insulin deficiency or resistance.
   (b) Hyperchloremic metabolic acidosis.
   (c) Hypertonicity (uncontrolled diabetes).
   (d) Massive tissue breakdown (rhabdomyolysis or tumor lysis syndrome).
   (e) Familial hyperkalemic periodic paralysis.
   (f) Medications.
      (i) β-Blockers,
      (ii) Digoxin (at toxic levels).
      (iii) Succinylcholine.
      (iv) Arginine.
      (v) Lysine.
5. Excess potassium administration.
   (a) Total parenteral nutrition.
   (b) Potassium supplements.
   (c) Diet or enteral feeds.
   (d) RBC transfusion.
   (e) Penicillin G potassium.

ACE is angiotensin converting enzyme; NSAID is nonsteroidal anti-inflammatory drug; RBC is red blood cell.

30.6.2 Clinical Effects of Hyperkalemia

The ratio of intracellular to extracellular potassium is the major determinant of the resting membrane potential. Hyperkalemia decreases resting membrane potential facilitating depolarization and impairing repolarization. The symptoms of mild to moderate hyperkalemia are usually asymptomatic; however, the first presenting symptom may be a fatal cardiac arrhythmia. Clinical manifestations that can result from membrane potential effects in striated muscle include weakness, paresthesias, and ascending paralysis. Ascending paralysis is usually seen in patients with chronic renal insufficiency when the serum potassium exceeds 7.5 mEq/L.

The most consistent ECG finding of hyperkalemia is elevation in the T waves that are best seen in the precordial leads (lead II).

The effects of potassium on cardiac conduction is of greatest concern (■ Table 30.5). Hyperkalemia interferes with atrial, ventricular, and atrioventricular conduction pathways leading to arrhythmias. The risks of arrhythmias usually correlate with the degree of hyperkalemia, but arrhythmias are more likely to occur with rapid increases in serum potassium than with gradual increases. The most consistent ECG finding of hyperkalemia is increased T waves followed by widening of the QRS complex. There is no clear cutoff where arrhythmias will develop, but patients with serum potassium >6.0 mEq/L should be considered at risk for arrhythmias, and patients with levels exceeding 6.5 mEq/L or having electrocardiographic features should receive immediate treatment.

30.6.3 Treatment of Hyperkalemia

The treatment of hyperkalemia largely depends on both the etiology and severity of hyperkalemia. The presence of ECG changes or serum potassium exceeding 6.5 mEq/L requires immediate therapy (▶ Box 30.4). Calcium can reverse cardiac conduction abnormalities and should be administered if ECG changes are present. Calcium can be administered through a properly functioning peripheral intravenous line in the urgent situation, but a central venous

■ **Table 30.5** Electrocardiographic manifestations of hyperkalemia

Serum potassium level	Expected ECG abnormality
Mild hyperkalemia 5.5–6.5 mEq/L	Tall, tent-shaped ("peaked") T waves with narrow base, best seen in precordial leads (lead II)
Moderate hyperkalemia 6.5–8.0 mEq/L	Peaked T waves.
	Prolonged PR interval.
	Decreased amplitude of P waves.
	Widening of QRS complexes.
Severe hyperkalemia >8.0 mEq/L	Absence of P wave.
	Intraventricular blocks, fascicular blocks, bundle branch blocks, QRS axis shift.
	Progressive widening of the QRS complex resulting in bizarre QRS morphology.
	Eventual "sine wave" pattern (sinoventricular rhythm), ventricular fibrillation, asystole.

Box 30.4 Emergency Management of Hyperkalemia

1. Evaluation.
   (a) Confirm that potassium value is venous and non-hemolyzed.
   (b) Place patient on cardiac monitor (lead II) and obtain ECG.
2. Conduction abnormalities.
   (a) Calcium gluconate (10%) 100 mg/kg/dose (1 mL/kg/dose) over 3–5 min. Can be repeated in 15 min.
3. Serum potassium > 6.5 mEq/L.
   (a) *Move potassium into cells.*
      (i) Regular insulin 0.1 U/kg with 25% glucose (2 mL/kg) IV over 30 min. Onset of effect is 10–20 min with duration of 2–3 h.
      (ii) Albuterol nebulization 0.5% 0.25 mg/kg/dose over 10 min. Onset of action 20–30 min, duration 2–3 h. can be used in conjunction with insulin and glucose.
      (iii) Sodium bicarbonate 1 mEq/kg, only if hyperchloremic metabolic acidosis; onset of action is 1–3 h.
   (b) *Remove potassium from body.*
      (i) Sodium polystyrene (Kayexalate) 1 g/kg/dose orally or as retention enema. Response time is 1–6 h.
      (ii) Loop diuretic.
      (iii) Hemodialysis or peritoneal dialysis.
      (iv) Fludrocortisone.

line should be placed for ongoing therapy. The acute management of hyperkalemia also includes therapies that shift potassium intracellularly. Intravenous insulin and glucose and an inhaled β_2-adrenergic agent such as albuterol are acceptable first-line therapies in the treatment of hyperkalemia. Both agents lower serum potassium by 0.6–1 mEq/L within 30 min and have an additive affect when used together. Insulin is effective in all patients but has the disadvantage of potentially causing hypoglycemia. Albuterol's main advantage is that it can be administered quickly and repeatedly without the need for vascular access with minimal side effects. The main disadvantage of albuterol is that it is ineffective in 10–20% of patients. Sodium bicarbonate has recently lost favor in the acute management of hyperkalemia as it is relatively ineffective in the absence of severe acidosis, has a delayed onset of action of 1 h, lowers ionized calcium, and can cause fluid overload and hypernatremia.

Following the acute lowering of serum potassium by causing an intracellular shift, the next objective is to remove potassium from the body via urine, stool, or dialytic therapies. The preferred method of removing potassium from the body is via urinary losses, so measures should be undertaken to improve urinary flow. Prerenal causes of acute kidney injury should be promptly treated with volume expansion, obstructive causes should be corrected, and urinary flow should be optimized with diuretics. When potassium removal via urinary losses is not possible, the sodium polystyrene resin (Kayexalate) is indicated. Kayexalate removes 0.5–1.0 mEq of potassium in exchange for 2–3 mEq of sodium. The primary site of potassium removal is the colon. Gastric administration of Kayexalate can require 6 h for potassium removal, while a retention enema can be effective in 2–3 h. Kayexalate is unpalatable, and quick delivery of a significant volume to a child will likely require nasogastric administration

or a retention enema. Kayexalate can have serious intestinal complications in the preterm infant, in patients with ileus, and in the immunosuppressed and should be used with caution. Multiple reports of bowel necrosis, intestinal perforation, bowel impaction, and intestinal bezoars have been reported. Hemodialysis is a rapid and effective means of potassium removal when there is severe renal impairment and acutely rising serum potassium.

Two other oral cation exchange resins were recently FDA approved for the treatment of hyperkalemia in adults: Lokelma (sodium zirconium cyclosilicate) and Veltassa (patiromer). Both agents are powders that are suspended in water and are safer than Kayexalate without the gastrointestinal side effects. Lokelma would appear to be the only agent suitable for the treatment of acute hyperkalemia as it has a more rapid onset of action of 1 hour in comparison to Veltassa that has a 7-hour onset of action. Lokelma has nine times the potassium binding of potassium as Kayexalate; it is highly selective for potassium binding. There is no data on the use of Veltassa in children, though it may replace Kayexalate as the first-line oral agent to treat acute hyperkalemia. Both Veltassa and Lokelma are suitable for the management of chronic hyperkalemia in adults.

β_2-adrenergics are equally effective to the administration of insulin and glucose in acutely lowering serum potassium.

The chronic treatment of hyperkalemia consists of limiting exogenous potassium from dietary sources, medications, or intravenous fluids. Medications contributing to hyperkalemia such as potassium-sparing diuretics or ACE inhibitors should be discontinued.

30.7 Magnesium

30.7.1 Hypomagnesemia

Hypomagnesemia is a common electrolyte abnormality in the critical care setting occurring in up to 60% of patients. Hypomagnesemia can develop rapidly as there are no regulatory hormones for magnesium, and there is not a rapid exchange between extracellular magnesium and bone and cellular stores. Hypomagnesemia usually results from dietary depletion, gastrointestinal losses, or urinary losses. The most common causes of hypomagnesemia in the critical care setting are malnutrition, diarrhea, nasogastric suction, diuretic use, volume expansion, diuretic phase of acute kidney injury, osmotic diuresis from diabetes, and nephrotoxic medications such as aminoglycosides, amphotericin B, cyclosporine, and tacrolimus. Hypomagnesemia frequently develops following cardiac bypass due to chelation from free fatty acids and from citrate.

Symptomatic hypomagnesemia usually occurs in conjunction with other electrolyte abnormalities, such as hypokalemia, alkalosis, or hypocalcemia. Conditions that cause hypomagnesemia also causes renal potassium wasting resulting in a hypokalemic state that is refractory to potassium repletion. Severe symptomatic hypomagnesemia is almost always associated with hypocalcemia. Hypomagnesemia impairs calcium homeostasis by decreasing PTH release and causing PTH resistance. The primary neurological symptoms of hypomagnesemia are similar to hypocalcemia with tetany, seizures, and carpopedal spasm. Magnesium depletion also affects cardiac conduction with widening of the QRS complex, prolongation of the PR interval, and diminution of the T wave. Hypomagnesemia can cause ventricular arrhythmias in the setting of ischemic heart disease or congestive heart failure.

Significant hypomagnesemia is defined as a serum magnesium less than 1.2 mg/dL (0.4 mmol/L or 1 mEq/L). Patients with hypocalcemic-hypomagnesemic tetany or hypokalemic-hypocalcemic arrhythmias should be treated with magnesium sulfate infusion. A special indication for magnesium supplementation is torsades de pointes. The American Heart Association recommends using magnesium sulfate in the treatment of torsades de pointes or refractory ventricular fibrillation. Rapid magnesium infusions over 2 h for cardiac or CNS indications or over 30 min for status asthmaticus are well tolerated and can be rapidly effective. However, rapid infusions also result in increased urinary magnesium losses; thus, continuous supplementation is the best way to provide ongoing correction when indicated. Hypomagnesemia is suspected to impair glucose metabolism, so magnesium should be supplemented in diabetics with hypoglycemia. The preferred method of replacing magnesium is the enteral route via slow-release preparations such as magnesium chloride or gluconate. Large doses of enteral magnesium can result in diarrhea.

Symptomatic hypomagnesemia usually occurs simultaneously with hypocalcemia.

Magnesium supplementation is recommended as treatment for torsades de pointes.

30.7.2 Hypermagnesemia

Hypermagnesemia is a rare clinical occurrence that is usually the result of excess magnesium administration to patients with renal impairment. Magnesium in phosphate-binding salts or magnesium-containing laxatives should be avoided in patients with renal impairment. Symptoms of severe hypermagnesemia include hypotension, bradycardia, somnolence, respiratory depression, and ECG abnormalities. In patients with normal renal function, hypermagnesemia can usually be managed by discontinuing the magnesium supplements. Severe symptoms can be reversed quickly by administering intravenous calcium as a magnesium antagonist. For severe toxicity and renal impairment, hemodialysis may be indicated.

Intravenous calcium can acutely reverse the symptoms of severe hypermagnesemia.

30.8 Phosphorus

30.8.1 Hypophosphatemia

Phosphate is the most abundant intracellular anion with less than 1% present in the plasma. Phosphate is essential for bone mineralization, energy metabolism, and cellular structure and function. Hypophosphatemia can result from an acute transcellular shift in phosphorous or from true phosphorous depletion from increased urinary losses or decreased intestinal absorption. Common causes of a transcellular shift in phosphorous are respiratory alkalosis, insulin administration, recovery phase of diabetic ketoacidosis, or the refeeding phase of malnutrition. Phosphorous depletion is common in patients post renal transplantation, with tubulopathies such as the Fanconi syndrome or X-linked hypophosphatemic rickets, with malnutrition, burns, vitamin deficiency, or diarrhea. Continuous hemofiltration can cause severe phosphorous depletion if large amounts of phosphorous are not replaced parenterally.

Symptomatic hypophosphatemia develops when the serum phosphorous falls below 1 mg/dL (0.32 mmol/L). Most of the clinical symptoms can be explained by decreased intracellular adenosine triphosphate (ATP) compounds and reduced 2,3-diphosphoglycerate (2,3-DPG). Symptoms include peripheral neuropathy, metabolic encephalopathy, seizures, proximal myopathy, dysphagia, and ileus. Respiratory depression can develop, and patients can be difficult

to wean from the ventilator due to respiratory weakness. Cardiac arrhythmias and impaired contractility can develop.

Causes of hypophosphatemia include respiratory alkalosis, insulin administration, recovery phase of diabetic ketoacidosis, or the refeeding phase of malnutrition.

Hypophosphatemia can cause respiratory fatigue and may make it difficult to wean a patient off mechanical ventilation.

Hypophosphatemia is best treated orally with either sodium or potassium phosphate. Intravenous phosphorous administration can cause severe hypocalcemia, so it must be given slowly and with caution. Intravenous phosphorous infusions are usually not given unless the serum phosphorus is less than 1.5 mg/dL (0.48 mmol/L). Serum calcium and phosphorous levels must be followed closely if phosphorous infusions are to be administered.

30.8.2 Hyperphosphatemia

Causes of hyperphosphatemia in the critical care setting are renal failure, rhabdomyolysis, tumor lysis syndrome, or hemolysis.

Severe hyperphosphatemia can cause symptomatic hypocalcemia by causing calcium and phosphorous to precipitate.

Serum phosphorous levels are higher in children than adults due to a higher bone turnover rate. Phosphorous is primarily filtered in the kidney. Hyperphosphatemia can develop from either excess exogenous administration of phosphorous, endogenous release of phosphorous from bone or cells, or reduced renal excretion of phosphorus. The main causes of hyperphosphatemia in the critical care setting are rhabdomyolysis, tumor lysis syndrome, hemolysis, or renal failure. The primary clinical feature of severe hyperphosphatemia is symptomatic hypocalcemia. Hyperphosphatemia causes calcium to precipitate when the product of the serum calcium times the phosphorous exceeds 72 mg/dL. If severe hyperphosphatemia occurs in conjunction with renal insufficiency, hemodialysis may be required. Oral phosphorus-binding salts or calcium, magnesium, or aluminum is useful in more chronic hyperphosphatemia.

30.9 Metabolic Acidosis

Metabolic acidosis is defined as an arterial pH below 7.36 in association with a reduced plasma bicarbonate concentration. Severe metabolic acidosis is defined as an arterial pH below 7.2. In general, metabolic acidosis stimulates a rapid ventilatory response decreasing the $PaCO_2$. The normal respiratory response to a metabolic acidosis is a decrease in $PaCO_2$ of 1.2 mmHg for every 1.0 mEq/L reduction of serum bicarbonate to a minimum $PaCO_2$ of 10 mmHg. In the presence of a normal respiratory response, a serum pH <7.20 would be observed only with serum bicarbonate <10 mEq/L. A less than expected respiratory response constitutes a mixed acid-base disturbance.

A useful way to categorize the nature of a metabolic acidosis is based on the anion gap. Metabolic acidosis can be classified as having either a normal anion gap (hyperchloremic acidosis) or an elevated anion gap. A normal anion gap acidosis results from bicarbonate loss from urine or the stool without proportional loss of chloride or with exogenous chloride loads via non-bicarbonate-containing fluids (e.g., large volumes of 0.9% NaCl). A renal tubular acidosis also produces a normal anion gap acidosis when the kidney is unable to maintain serum pH via appropriate hydrogen excretion or bicarbonate reabsorption.

An elevated anion gap acidosis indicates an increased rate of endogenous acid generation, such as ketoacids or lactate, the addition of exogenous organic acids, or decreased renal capacity to excrete an acid load as is seen in renal failure.

The anion gap is calculated as follows:

$$\text{Anion gap} = [\text{Na}] - ([\text{Cl}] + [\text{HCO}_3])$$

A normal anion is typically 7–12 mEq/L but may be as high as 15 mEq/L in children younger than 2 years of age.

The negatively charged unmeasured particles constituting the anion gap are primarily albumin; therefore, the anion gap must be corrected for a low serum albumin concentration. The anion gap decreases by 2.5 mEq/L for every 1 g/dL reduction in serum albumin from normal. When the serum albumin falls to below 2 g/dL, the anion gap can be zero or less. Thus, to correct the anion gap for low serum albumin, 2.5 mEq/L must be added to the observed anion gap for every 1 g/dL decrease in serum albumin below 4 g/dL.

The PCO_2 falls an average of 1.2 mmHg for every 1 mEq/L reduction in serum bicarbonate.

The anion gap decreases by 2.5 mEq/L for every 1 g/dL decrease in serum albumin below 4 g/dL.

30.9.1 Hyperchloremic Metabolic Acidosis (▸ Box 30.5)

Box 30.5 Non-anion Gap Acidosis

1. Gastrointestinal bicarbonate loss.
   (a) Diarrhea.
   (b) Small bowel, pancreatic, or biliary drainage.
   (c) Uterosigmoidostomy.
   (d) Cholestyramine (bile acid diarrhea).
2. Renal tubular acidosis (RTA).
   (a) Proximal renal tubular acidosis (type 2 RTA).
   (b) Classic distal RTA (type 1 RTA).
   (c) Mineralocorticoid deficiency or resistance (type 4 RTA).
   (d) Carbonic anhydrase inhibitors.
3. Other.
   (a) Dilutional acidosis (rapid saline infusion).
   (b) Post-hypocapnic state.

30.9.1.1 Gastrointestinal Losses of Bicarbonate

Gastrointestinal secretions beyond the stomach are rich in bicarbonate. Large intestinal fluid losses of bicarbonate result in a normal anion gap acidosis with hyperchloremia. The latter occurs because the fall in serum bicarbonate must be accompanied by a corresponding increase in serum chloride to maintain electroneutrality. The normal renal response to metabolic acidosis is to generate an acid urine ($pH \leq 5.5$). If hypokalemia or severe acidosis is present, significant urinary NH_4 excretion can paradoxically result in a urine pH greater than 6.0. The renal excretion of NH_4 can be estimated by measuring the urine anion gap. The equation for the urine anion gap is:

$$\text{Urine anion gap} = \text{Urine}\left(\left[\text{Na}\right]+\left[\text{K}\right]\right)-\text{Cl}$$

A negative urine anion gap indicates urinary NH_4 excretion and confirms a normal renal response to metabolic acidosis even in the face of a urine $pH > 5.5$.

The normal renal response to metabolic acidosis is to excrete NH_4 in the urine. This can be estimated by measuring the urine anion gap; a negative gap confirms NH_4 excretion.

30.9.1.2 Dilutional Acidosis

A common cause of a normal anion gap metabolic acidosis in the pediatric critical care unit is due to the rapid expansion of the extracellular space with large amount of intravenous fluids that do not contain bicarbonate. Large amounts of NaCl administration, as fluid resuscitation, can dilute the serum bicarbonate and result in acidosis. The rapid infusion of saline-containing fluids causes only a modest decrease in the serum bicarbonate despite the fact that saline-containing intravenous fluids have a pH of between 4 and 5 because of the intracellular buffering system and the renal response to acidosis.

Rapid expansion of the extracellular space with non-bicarbonate-containing fluids can result in a dilutional acidosis.

Distal renal tubular acidosis has a urine pH greater than 5.5 and a positive urine anion gap, indicating impaired urine NH_4 excretion.

30.9.1.3 Renal Tubular Acidosis

Renal tubular acidosis (RTA) describes a group of conditions characterized by either a defect in bicarbonate reabsorption or impaired hydrogen ion excretion. Renal tubular acidosis is classified in three main categories: proximal RTA (type 2), distal RTA (type 1), and hyperkalemic RTA (type 4). These conditions can be either hereditary or acquired, can result from a variety of medications or toxins, and are associated with numerous disease states. Proximal RTA is caused by impaired bicarbonate reabsorption in the proximal tubule with normal distal urine acidification. In proximal RTA, the urine pH may be lower than 5.5, and the urine anion gap is usually negative indicating normal urine NH_4 excretion. Treatment of proximal RTA typically requires large amounts of bicarbonate. Distal RTA results from impaired hydrogen ion excretion in the distal tubule. The urine pH is generally greater than 5.5, and urine anion gap is positive indicating impaired urine NH_4 excretion. The acidosis is usually corrected with relatively small doses of bicarbonate. A hyperkalemic RTA is primarily due to mineralocorticoid resistance or deficient states. The urine pH is typically greater than 5.5, and the urine anion gap is positive. Treatment consists of either mineralocorticoid or bicarbonate replacement.

30.9.2 Elevated Anion Gap Acidosis (▸ Box 30.6)

An elevated anion gap acidosis can result from three causes: increased endogenous organic acid production, impaired renal excretion of organic acids, and the ingestion of organic acids. The most common cause of elevated anion gap acidosis in the critical care setting is from endogenous organic acid production, specifically lactate and ketoacids. Diabetic ketoacidosis is discussed elsewhere in this text.

Box 30.6 Elevated Anion Gap Acidosis

1. Lactic acidosis.
   - (a) L-lactic acidosis.
     - (i) Hypoperfusion/hypoxia.
     - (ii) Inborn errors of metabolism.
     - (iii) Cyanide intoxication.
     - (iv) Seizures.
     - (v) Severe exercise.
     - (vi) Alcohol.
   - (b) D-lactic acidosis.
     - (i) Short gut syndrome.
2. Ketoacidosis.
   - (a) Diabetic ketoacidosis.
   - (b) Alcoholic ketoacidosis.
   - (c) Starvation ketoacidosis.
3. Renal failure.
4. Toxins.
   - (a) Ethylene glycol.
   - (b) Methanol.
   - (c) Salicylates.
   - (d) Paraldehyde.

30.9.2.1 Lactic Acidosis

Lactate production results from the anaerobic metabolism of pyruvate (▶ Chap. 2). The most common cause of L-lactic acidosis is from oxygen-deficient states such as hypoxia and hypoperfusion which are frequently seen in septic and cardiogenic shock. This is termed type A (fast) lactic acidosis. Lactic acidosis that occurs in the absence of hypoxia is termed type B (slow) lactic acidosis. Examples of type B lactic acidosis are inborn errors in metabolism, cyanide intoxication from nitroprusside, or severe exercise. An unusual form of lactic acidosis is D-Lactic acidosis which can be seen in short gut syndrome or malabsorption states. In these diseases, bacteria metabolize carbohydrates to D-lactic acid that is then systemically absorbed. Serum lactate levels do not measure the presence of D-lactate. The primary treatment of lactic acidosis is to treat the underlying disease state. Laboratory tests measure lactate and not lactic acid; there are other causes of increased lactate that are not associated with a metabolic acidosis, such as increased gluconeogenesis.

Cyanide intoxication from nitroprusside can result in lactic acidosis due to impaired mitochondrial oxygen utilization.

30.9.2.2 Toxic Ingestions

Life-threatening poisonings that can cause an elevated anion gap acidosis deserve specific mention. Aspirin (acetylsalicylic acid) results in both a keto-acidosis and lactic acidosis by uncoupling oxidative phosphorylation which results in anaerobic metabolism. Methanol, a common component of varnish, is metabolized to formaldehyde than to formic acid. Ethylene glycol, a common component of antifreeze, is metabolized to glycolic acid and oxalic acid. A key feature of methanol and ethylene glycol ingestion is an elevated osmolar gap, where the measured serum osmolality exceeds the calculated osmolality by greater than 25 mOsm/L.

30.9.3 Clinical Effects of Acidemia (▶ Box 30.7)

Severe acidosis is rarely lethal in an otherwise healthy individual in the absence of cardiac dysfunction. Complication-free survival has been reported in individuals with a pH less than 6.8. Severe metabolic acidosis can cause arrhythmias, hypotension, and hyperkalemia. Metabolic acidosis lowers systemic vascular resistance, but this is often offset by increased sympathetic nervous system activation. Metabolic acidosis results in an efflux of cellular potassium which may result in hyperkalemia. For reasons that are unclear, hyperkalemia is primarily seen with a hyperchloremic acidosis and not with an elevated anion gap acidosis.

Box 30.7 Clinical Effects of Acidemia

1. Cardiovascular.
   (a) Arrhythmias.
   (b) Hypotension.
   (c) Resistance to vasopressors.
   (d) Venoconstriction with centralization of blood volume.
2. Central nervous system.
   (a) Decreased sensorium.
3. Gastrointestinal.
   (a) Gastric atony.
4. Hepatic.
   (a) Reduced hepatic blood flow.
5. Metabolic.
   (a) Shift of oxyhemoglobin dissociation curve increasing tissue oxygen release.
   (b) Insulin resistance.

30.9.4 Treatment of Metabolic Acidosis with Bicarbonate: The Pros and Cons

Metabolic acidosis should not be viewed as a disease but as a symptom of an underlying disorder. As such, the primary goal of therapy is to treat the underlying condition. When severe acidosis is present (pH <7.2), bicarbonate therapy may be indicated in selected cases.

The safety and efficacy of bicarbonate therapy largely depend on the etiology of the acidosis. Bicarbonate therapy can be beneficial in severe hyperchloremic acidosis, pH <7.2, and total CO_2 < 8 mEq/L, such as that seen with either large gastrointestinal or urinary losses of bicarbonate. The body's metabolic response to hyperchloremic acidosis is the renal regeneration of bicarbonate. This can be a slow process taking days. If there are ongoing gastrointestinal losses or renal dysfunction, the body may not be capable of repairing the acidosis. Under these circumstances, addition of sodium bicarbonate to intravenous fluids is indicated both to relieve the dyspnea of respiratory compensation and to improve pH for organ function. The aim of acute treatment of severe hyperchloremic acidosis is a serum bicarbonate of 10 mEq/L, subsequently followed by a slow correction to normal.

The use of sodium bicarbonate to treat an elevated anion gap acidosis is more controversial. The main indication for using bicarbonate therapy is presumably to improve cardiac contractility. Although not supported with consistent data, the effects of endogenous or exogenous catecholamines can be depressed in the face of severe acidosis. Most data show that acute respiratory acidosis has a greater negative inotropic effect compared with metabolic acidosis. Based on observations, many intensivists believe that some bicarbonate supplementation in the presence of severe anion gap acidosis results in more rapid circulatory recovery, although to be effective, ventilation must be adequate to assure that the CO_2 generated from bicarbonate's buffering action is eliminated.

There are three conditions where bicarbonate therapy is of questionable benefit and may be deleterious: diabetic ketoacidosis, lactic acidosis, and cardiac arrest.

30.9.4.1 Diabetic Ketoacidosis

In theory, an elevated anion gap acidosis should correct rapidly once the underlying metabolic defect is corrected as the organic anion will be metabolized to bicarbonate. In diabetic ketoacidosis (DKA), acid-base balance is restored with slow hydration and insulin. The theoretical reason to use bicarbonate in DKA is that severe metabolic acidosis can cause insulin resistance, and the addition of bicarbonate may hasten the recovery. However, studies in both children and adults found no benefit from adding bicarbonate to the treatment of DKA in correcting hyperglycemia, clearing ketoacids, shortening hospital stay, or decreasing complications of DKA. In fact, bicarbonate use was found to be a risk factor for the development of cerebral edema.

30.9.4.2 Lactic Acidosis

Bicarbonate therapy in lactic acidosis can worsen cardiac function. In most clinical settings, lactic acidosis is best treated by reversing the cause rather than administration of sodium bicarbonate.

Lactic acidosis can have serious systemic effects, decreasing hepatic blood flow and cardiac output, which results in decreased lactate clearance and tissue perfusion. In theory, bicarbonate therapy might improve some of the adverse systemic effects of lactic acidosis. However, many laboratory studies found that bicarbonate administration in lactic acidosis is not beneficial and in fact has many deleterious consequences. A reasonable criticism of many animal studies is the magnitude and rapidity of the bicarbonate correction of acidosis employed, and there are clinical studies attesting to the safety of slower infu-

sions of smaller doses sodium bicarbonate. Rapid infusion of bicarbonate appears to further decrease cardiac output by worsening the intracellular pH via increased CO_2 generation, lowering the ionized calcium, and further stimulating lactate production. Indeed, at the bedside in the intubated patient with end-tidal CO_2 monitoring, one can observe the rise in CO_2 elimination in response to rapid bicarbonate administration and the lack of change in end-tidal CO_2 with slower infusion. The large amount of bicarbonate therapy necessary to correct a severe lactic acidosis can result in hypernatremia and fluid overload as sodium bicarbonate is hyperosmolar; the Na concentration in 8.4% sodium bicarbonate is 1000 mEq/L. Bicarbonate therapy in the treatment of severe lactic acidosis in conjunction with high volume hemofiltration may obviate some of these problems in that lactate removal can be achieved, and large amounts of bicarbonate can be administered without the deleterious consequences of hypernatremia and fluid overload.

30.9.4.3 Cardiac Arrest

Bicarbonate therapy had been the standard treatment in cardiac arrest, but data has revealed that it is deleterious. The American Heart Association no longer recommends bicarbonate therapy in cardiac arrest. Bicarbonate therapy is particularly dangerous in metabolic acidosis if there is an additional component of respiratory acidosis. Bicarbonate therapy increases CO_2 production resulting in increased intramyocardial and cardiac venous pCO_2, lowering intracellular pH and reducing cardiac function.

Bicarbonate therapy is not recommended in the treatment of cardiac arrest.

A central venous blood gas may be helpful to assess if bicarbonate therapy is resulting in increased CO_2 retention.

30.10 Metabolic Alkalosis

Metabolic alkalosis is defined as an arterial pH greater than 7.44 associated with an increase in plasma bicarbonate. Severe alkalosis is defined as an arterial pH exceeding 7.55. The normal respiratory response to metabolic alkalosis is to decrease ventilation, though in the absence of oxygen supplementation, this response is limited by hypoxemia from hypoventilation. In the presence of oxygen supplementation as occurs in the PICU, this hypoventilation response is not blunted. An increase in $PaCO_2$ of 0.5–0.7 mmHg can be expected for every 1 mEq/L increase in bicarbonate. For arterial pH to exceed 7.55 in the presence of a normal respiratory response in supplemental oxygen, the serum bicarbonate would have to exceed 45 mEq/L. An abnormal respiratory response would result in a mixed acid-base disorder.

Metabolic alkalosis is primarily due to two causes: either chloride depletion (chloride-sensitive alkalosis) or potassium depletion (chloride-resistant alkalosis) (► Box 30.8). Excess bicarbonate administration alone usually does not result in sustained alkalosis unless there is renal dysfunction as excess bicarbonate would be excreted in the urine. In order for a sustained alkalosis to develop, there must be both a mechanism of generating bicarbonate and an ongoing renal mechanism to reclaim bicarbonate and prevent bicarbonate excretion. An alkalosis can be generated by either proton loss via gastric acid secretion or urinary NH_4 losses or excess base gain by alkali administration or dissolution of bone apatite. Maintenance of alkalosis results from a paradoxical aciduria with ongoing renal bicarbonate reabsorption.

The normal respiratory response to metabolic acidosis is for the $PaCO_2$ to increase by 0.5–0.7 mmHg for each 1 mEq/L rise in serum bicarbonate.

Patients with a sustained metabolic alkalosis usually have a paradoxical aciduria.

Box 30.8 Etiology of Alkalosis

1. Chloride depletion (chloride-sensitive alkalosis).
   (a) Gastric losses: Repeated emesis, nasogastric suctioning, bulimia.
   (b) Chloruretic diuretics: Loop diuretic, thiazide diuretics.
   (c) Diarrheal states: Congenital chloride diarrhea, villous adenoma, post-hypercapnic state.
   (d) Dietary chloride deprivation: Chloride-deficient infant formula.
   (e) Gastrocystoplasty.
   (f) Cystic fibrosis: High sweat chloride losses.
2. Potassium depletion/mineralocorticoid excess.
   (a) Primary hyperaldosteronism.
   (b) Apparent mineralocorticoid excess: Hydroxylase deficiencies, excess licorice (glycyrrhizic acid), Liddle syndrome.
   (c) Secondary aldosteronism: Adrenal corticosteroid excess.
   (d) Bartter and Gitelman syndromes.
3. Hypercalcemic syndromes.
   (a) Milk alkali syndrome.
   (b) Hypercalcemia of malignancy.
4. Other.
   (a) Penicillin antibiotics.
   (b) Bicarbonate administration with renal failure.
   (c) Recovery from starvation.

30.10.1 Chloride-Sensitive Alkalosis

The primary cause of severe alkalosis in the critical care setting that may require immediate therapy is due to chloride depletion from either massive gastric secretion loss or diuretic administration. Bicarbonate generated as a consequence of gastric acid losses to maintain electroneutrality, such as that seen with persistent emesis, can result in severe alkalosis. Loop and thiazide diuretics, which function by inhibiting chloride reabsorption, causes urinary losses of sodium, chloride, and water resulting in severe alkalosis. Diuretics increase sodium delivery to the distal nephron, leading to increased sodium-potassium and sodium-hydrogen exchange causing accelerated urinary potassium and proton secretion. The accompanying extracellular volume depletion stimulates increased renin and aldosterone release which further causes urinary potassium and proton secretion. Potassium depletion augments bicarbonate reabsorption in the proximal tubule and stimulates urinary NH_4 excretion. Aggressive diuretic use in edematous states, with a combination of a loop diuretic and metolazone, can cause a rapid decrease in the extracellular volume and the volume of distribution of bicarbonate resulting in a "contraction alkalosis."

A urine chloride less than 10 mEq/L is suggestive of chloride-sensitive alkalosis.

In conditions of chloride depletion, the alkalosis is maintained by a combination of volume depletion, which increases proximal tubule reabsorption of bicarbonate, and chloride depletion, which results in decreased distal tubule delivery of chloride that ultimately impairs distal tubule bicarbonate excretion. Chloride depletion, and not volume depletion, is the primary mechanism sustaining the alkalosis as the alkalosis can be corrected with chloride replacement in the absence of volume repletion. Chloride depletion alkalosis can usually be diagnosed by measuring the urinary chloride concentration, which is usually less than 10 mEq/L.

30.10.2 Chloride-Resistant Alkalosis

In chloride-resistant alkaloses, chloride deficiency plays no role in accelerated tubular H+ secretion and subsequent bicarbonate reabsorption. There is no loss of chloride-rich fluid, and usually no volume depletion. The main abnormalities seen in chloride-resistant alkalosis are mineralocorticoid excess and/or hypokalemia. The combination of hypokalemia and mineralocorticoid excess results in a moderate alkalosis. In general, the alkalosis seen from mineralocorticoid excess is usually not severe. Mineralocorticoid excess can be primary, as seen with primary hyperaldosteronism with suppressed renin, or secondary, as seen with Bartter's and Gitelman's syndrome with elevated renin and aldosterone concentrations. Mineralocorticoid excess stimulates sodium reabsorption and further potassium and proton secretion. In chloride-resistant alkalosis, the urinary chloride is typically greater than 30 mEq/L, and there is hypokalemia with ongoing urinary potassium losses.

Severe hypokalemia results in potassium movement from cells and reciprocal entry of Na + and H+. This intracellular H+ entry raises plasma HCO_3-. At the tubular level, the increased intracellular H+ facilitates tubular H+ secretion that further augments the alkalosis.

Hypokalemia is the main contributing factor to metabolic alkalosis when volume expansion with saline is ineffective.

30.10.3 Post-hypercapnic Metabolic Alkalosis

Chronic respiratory acidosis results in a compensatory metabolic alkalosis whereby there is an increase in renal H^+ excretion with obligate retention of bicarbonate. In addition, co-excretion of Cl^- with H^+ may also lead to hypochloremia. This results in a state of total body HCO_3^- excess and Cl^- depletion. The rapid correction of hypercapnia results in post-hypercapnic metabolic alkalosis as the nephron is unable to rapidly excrete the previously retained bicarbonate. Thus, it is imperative that correction of chronic CO_2 retention occurs slowly. Rapid reduction of the pCO_2 may result in profound elevations in pH with concomitant deleterious physiologic effects. These include decreased coronary and cerebral blood flow, decreased oxygen release at distal tissues secondary to a leftward shift of the oxyhemoglobin dissociation curve, and decreased availability of ionized calcium. The renal response is to excrete $NaHCO_3$, but in order to achieve this, NaCl must be provided to prevent volume depletion. In the absence of NaCl administration, the alkalosis may persist as a result of volume contraction.

30.10.4 Adverse Clinical Effects of Alkalemia (▸ Box 30.9)

Severe alkalemia, arterial pH greater than 7.55, can have significant physiologic consequences. Alkalemia causes arteriolar constriction that may compromise cerebral and myocardial perfusion. Neurological symptoms include headache, tetany, seizures, confusion, apathy, and neuromuscular irritability. The systemic effects of respiratory alkalosis are more severe than metabolic alkalosis. Some of the neurological manifestations of metabolic alkalosis may be a consequence of associated electrolyte abnormalities such as hypocalcemia and hypokalemia. Severe alkalemia may also depress respiratory drive.

Severe alkalemia can decrease cerebral and cardiac perfusion.

Box 30.9 Adverse Clinical Effects of Alkalemia

1. Cardiovascular.
   (a) Arteriolar constriction with reduction in coronary artery blood flow.
   (b) Decreased ionized calcium with decreased myocardial inotropy.
   (c) Shifts oxyhemoglobin dissociation curve, reducing tissue oxygen release.
2. Respiratory.
   (a) Hypoventilation with attendant hypercapnia and hypoxemia.
3. Metabolic.
   (a) Stimulation of anaerobic glycolysis and organic acid production.
   (b) Hypokalemia.
   (c) Decreased plasma ionized calcium concentration.
   (d) Hypomagnesemia and hypophosphatemia.
4. Cerebral.
   (a) Reduction in cerebral blood flow.
   (b) CNS irritability with tetany, seizures, lethargy, delirium, and stupor.

30.10.5 Treatment of Metabolic Alkalosis

The treatment of metabolic alkalosis largely depends on the etiology. The underlying cause of alkalosis should be determined and corrected. Usual therapies include correction of volume depletion, chloride depletion, and potassium depletion and promoting bicarbonate excretion.

If volume depletion is present, then volume expansion with 0.9% sodium chloride is indicated. If alkalosis and volume depletion are due to large amounts of gastric drainage, a proton pump inhibitor may be helpful. If diuretics are the cause, then decreasing the diuretic dose or temporarily discontinuing the diuretic may be necessary. A chloride-sensitive alkalosis generally responds to sodium chloride and potassium chloride supplementation. In cases of severe life-threatening alkalemia (pH >7.6) where sodium chloride may be contraindicated, such as with congestive heart failure, hydrochloric acid (HCl) administration may be warranted. HCl is sclerosing and hyperosmolar and should not be infused through a peripheral line. A 1 mEq/kg dose of HCl lowers the plasma bicarbonate by about 2 mEq/L. Alternatively, ammonium chloride can be used to correct severe hypochloremic alkalosis. Acetazolamide, a carbonic anhydrase inhibitor, can be useful in managing a metabolic alkalosis where large amount of saline may be contraindicated such as in the edematous patient. Acetazolamide inhibits proximal sodium bicarbonate reabsorption, thereby aiding in the correction of both the alkalosis and the fluid overload.

A chloride-resistant alkalosis that is primarily due to potassium depletion generally responds well to potassium chloride supplementation. Potassium chloride should preferably be administered by the oral route divided in three to five daily doses. In the diuretic-dependent patient, the addition of a potassium-sparing diuretic such as spironolactone may be useful in preventing ongoing potassium loss.

Review Questions

1. A 10 kg child is admitted for isonatremic dehydration. Following an initial fluid bolus total of 40 mL/kg, the remaining deficit should be replaced with what type of continuous intravenous fluids?
   A. 0.2% normal saline
   B. 0.2% normal saline with 40 mEq of sodium acetate added to each liter of fluid
   C. 0.45% normal saline
   D. 0.45% normal saline with 10 mEq of sodium acetate added to each liter of fluid
   E. 0.9% normal saline.

2. A neurosurgical patient develops hypernatremia while receiving 0.9% normal saline. Which of the following is the MOST effective way of diagnosing diabetes insipidus in this setting?
   A. Measuring a plasma copeptin level.
   B. Measuring a spot urine osmolality.
   C. Measuring urine tonicity (sodium + potassium).
   D. Measuring urine volume.
   E. Performing magnetic resonance imaging (MRI) of the hypothalamus and pituitary.

3. Which of the following is the single most important factor in the development of hospital-acquired hyponatremia?
   A. Cardiac disease.
   B. Fluid retention.
   C. Hypotonic fluid administration.
   D. Renal disease.
   E. Subclinical volume depletion.

4. A 5 kg infant with bronchiolitis is transferred to the pediatric intensive care unit actively seizing and is found to have a serum sodium of 123 mEq/L. Which of the following is the MOST appropriate therapy?
   A. 0.9% normal saline bolus (10 mL/kg)
   B. 3% normal saline bolus of 10 mL over 10 min
   C. 3% normal saline infusion at 5 mL/h
   D. Intravenous lorazepam (0.5 mg).
   E. Intravenous mannitol (5 g) over 15 min.

5. A patient with nephrotic syndrome is found to have a total serum calcium level of 6.8 mg/dL with a serum albumin of 2.0 g/dL. What is the corrected total serum calcium?
   A. 6.0
   B. 7.8
   C. 8.4
   D. 9.4
   E. 10.0.

6. Hypokalemia is MOST likely to produce a serious arrhythmia in the setting of which of the following clinical conditions?
   A. Cardiac disease.
   B. Hypocalcemia.
   C. Hyponatremia.
   D. Mitochondrial disease.
   E. Sepsis.

7. A 7-year-old male with a potassium level of 6.7 mEq/L developed significant changes on his electrocardiogram consisting of peaked T waves and prolongation of his QRS interval. Which of the following interventions is the MOST appropriate immediate course of action?
   A. Hemodialysis.
   B. Inhaled beta-adrenergic agonist.
   C. Intravenous calcium administration.
   D. Intravenous insulin and dextrose infusion.
   E. Sodium polystyrene resin retention enema.

8. A patient with nephrotic syndrome also has diarrhea and is found to have a total CO_2 of 12 mEq/L, serum albumin of 1.0 g/dL, and a calculated anion gap of 5 mmol/L. What is the corrected anion gap?
   A. 6
   B. 8
   C. 10
   D. 12
   E. 16

9. A 4-month-old is admitted to the pediatric intensive care unit following cardiopulmonary arrest. Point-of-care blood testing reveals a pH 7.01, $PaCO_2$ 32 mm Hg, PaO_2 347 mm Hg, base deficit (−27 mEq/L), hemoglobin of 9.7 g/dL, and an ionized calcium level of 1.05 mmol/L. The infant receives two 20 mL/kg fluid boluses of 0.9% normal saline, is treated with sodium bicarbonate (1 mEq/kg), and is started on an infusion of dobutamine. Repeat point-of-care testing reveals a pH 7.21, $PaCO_2$ 38 mm Hg, PaO_2 163 mm Hg, and a base deficit (−12). Assuming that no calcium was administered, and based solely on the blood gas result, the ionized calcium level on that point-of-care testing should MOST closely approximate which of the following?
   A. 0.73 mmol/L
   B. 0.85 mmol/L
   C. 1.05 mmol/L
   D. 1.20 mmol/L
   E. 1.37 mmol/L.

Answers

1. E
2. B
3. C
4. B
5. C
6. A
7. C
8. D
9. A

Suggested Reading

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Acute Kidney Injury

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Contents

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Learning Objectives

After reading this chapter, the reader should be able to:

- Discuss the interpretation and limitations of serum creatinine levels as an indicator of renal function in children of different ages.
- Describe the major causes of acute kidney injury in children and how the epidemiology of acute kidney injury has changed over time.
- Distinguish between pre-renal, intrinsic, and post-renal causes of acute kidney injury using appropriate laboratory tests and imaging studies.
- Describe the major manifestations of acute kidney injury in children.
- Discuss the management of the major perturbations of homeostasis caused by acute kidney injury and the controversies surrounding some of the traditional interventions in acute kidney injury, such as diuretics and low-dose dopamine infusion.
- Discuss the indications for renal replacement therapy and the clinical issues that must be considered when choosing between different renal replacement modalities.
- Discuss interventions that may prevent or modify the course of acute kidney injury.
- Discuss the effect of acute kidney injury on the choice and dosing of drugs.
- Describe the effect of acute kidney injury on the management and outcome of other diseases and the effect of other disease processes on renal function.
- Discuss the prognosis of children with acute kidney injury.

31.1 Assessing Renal Function in Children

Creatinine generation is proportional to muscle mass, and therefore, serum levels are influenced by age, gender, and nutritional status in addition to renal clearance.

The serum creatinine value is the most frequently used marker of glomerular filtration rate (GFR) in the clinical setting because it is an easily obtained laboratory measurement with a long history of clinician familiarity and use. However, in evaluating renal function in children, there are many considerations one must weigh when interpreting serum creatinine values. First, serum creatinine is proportional to muscle mass, and serum creatinine in children rises with age as muscle mass increases. Therefore, an understanding of expected serum creatinine levels for age and gender is crucial for interpretation of clinical data (Table 31.1). The relationship between serum creatinine level and muscle mass may lead to an overestimation of renal function in nutritionally depleted children with decreased muscle mass and decreased creatinine production, who may have a "normal" serum creatinine level in the face of significant renal impairment. Second, renal function undergoes maturation during infancy. Nephrogenesis is not complete until about 34–36 weeks gestation. Premature infants will therefore have a very low GFR and serum creatinine levels that are elevated compared to more mature infants. Thus, a serum creatinine of 1.4 mg/dL is normal in the 1st week of life for premature infants

Table 31.1 Expected serum creatinine levels (mg/dL) for age and gender

	1 month–2 years	3–5 years	6–9 years	10–11 years	12–15 years	16–18 years
Male	0.2–0.4	0.2–0.5	0.3–0.6	0.4–0.7	0.4–0.9	0.5–1.0
Female	0.2–0.4	0.2–0.5	0.3–0.6	0.4–0.7	0.4–0.8	0.4–0.9

between 25 and 28 weeks gestation, falling to 0.9 mg/dL between the 2nd and 8th weeks of life and reaching a level of 0.4 mg/dL comparable to more mature infants thereafter. Premature infants between 29 and 34 weeks gestation have a serum creatinine of 0.9 mg/dL during the 1st week of life, 0.7 mg/dL between the 2nd and 8th week, and 0.4 mg/dL thereafter. Even term infants undergo significant hemodynamic changes affecting renal perfusion and glomerular filtration so that serum creatinine levels fall progressively during the first week or two of life, ultimately attaining values detected in older infants. Term infants have a serum creatinine of 0.6 mg/dL in the 1st week of life, falling to 0.4 mg/dL after the 2nd week and remaining fairly constant for the first 2 years of life. Finally, the low serum creatinine found in young children can be more difficult to measure accurately depending on the assay employed. Therefore, creatinine levels may vary greatly from laboratory to laboratory. Enzymatic determination of creatinine concentration is more accurate than alkaline picrate assays at the low serum levels encountered in the younger pediatric population. The method used by the hospital laboratory to measure creatinine should be considered when comparing a patient's creatinine level to published norms.

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In the steady state, GFR in children can be estimated by the formula $k \times (\text{Ht})/\text{sCr}$.

The gold standard for measuring GFR is inulin clearance. However, this is not practical in the clinical setting. GFR can be approximated by determination of the creatinine clearance using a 24-h urine collection because creatinine excretion occurs primarily by filtration at normal levels of renal function. However, these collections are often cumbersome to perform, prone to errors, and, at lower levels of renal function, lead to overestimation of GFR in the face of significant renal impairment due to tubular secretion of creatinine accounting for a much greater proportion of total creatinine excretion. Formulas developed for estimating GFR from serum creatinine in adults (Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), and CKD-EPI formulas) are not appropriate for use in children. In children, GFR is directly proportional to the height of the patient and indirectly proportional to the serum creatinine and, thus, can be estimated using the modified Schwartz formula:

$$\text{eGFR} = (\text{k} \times \text{Ht})/\text{sCr},$$

where *eGFR* is the estimated GFR (mL/min/1.73 M^2), *k* is a constant of 0.413 for children 1 to 16 years of age, *Ht* is the height (centimeters), and *sCr* is the serum creatinine concentration (mg/dL). For older teenagers and young adults, the modified Schwartz formula tends to underestimate, and the CKD-EPI formula tends to overestimate true GFR, while the average of the two formulas can be used to give a more accurate estimate of true GFR in this population. Since creatinine generation is proportional to muscle mass, in conditions of reduced muscle mass, as may be observed in patients with severe malnutrition, muscular dystrophy, anorexia, prolonged immobilization, malignancies, or limb amputations, serum creatinine will be low, and GFR will be overestimated using creatinine-based formulas.

Serum cystatin C, a low-molecular-weight proteinase inhibitor that is filtered at the glomerulus and reabsorbed and metabolized by the proximal tubule, has been proposed to be a more reliable marker of GFR than creatinine because it is not dependent on muscle mass. In patient populations with less muscle mass, cystatin C is the desirable method to assess kidney function. However, serum cystatin C levels can be affected by inflammatory states, steroid use, and thyroid dysfunction. Cystatin C was found to be a reliable measure of kidney function in children with acute kidney injury (AKI) related to aminoglycoside use. Creatinine- and cystatin C-based equations incorporating variables such as height, gender, and blood urea nitrogen (BUN) have been proposed to increase the accuracy and precision of the calculations. Calculators for determining creatinine and cystatin C estimates of GFR are available on the Internet.

31.2 Definition of Acute Kidney Injury

Acute kidney injury is the abrupt loss of renal function manifesting as retention of nitrogenous wastes and the inability to maintain fluid and electrolyte homeostasis. Traditionally, adult studies have used a specific creatinine value above which a patient was considered to have AKI. Given the variable and lower values of creatinine in children, such a definition is not useful in pediatrics. A rise in serum creatinine by a particular percentage has been used in other adult studies, and a rise in serum creatinine by 50% has been used as a definition of acute renal failure for children as well. However, glomerular filtration rate may decline by more than 50% before a rise in serum creatinine is observed. AKI represents a perturbation of the steady state with a decrease in excretion of creatinine compared to its production leading to a rising serum creatinine. Early in the course of AKI, GFR is generally decreased to a much greater extent than is suggested by the level of the serum creatinine until a new steady state is attained.

Various efforts to standardize the definition of AKI have been proposed including the RIFLE (*R*isk, *I*njury, and *F*ailure and two measures of outcome *L*oss and *E*nd-Stage kidney injury) and AKIN (*A*cute *K*idney *I*njury *N*etwork) criteria and the pRIFLE modifications to make the RIFLE criteria applicable to the pediatric population. To address shortcomings in each of these models, the criteria were combined in a proposal by the Kidney Disease Improving Global Outcomes (KDIGO) group. These criteria are applicable to AKI in children and are presented here.

KDIGO definition and staging for AKI		
AKI stage	**Serum creatinine**	**Urine output**
1	Increased creatinine by 0.3 mg/dL within 48 h *or* Increase in creatinine by 150% to <200% from previous trough	<0.5 mL/kg/h for 6–12 h
2	Increase in creatinine by 200% to <300% of previous trough	<0.5 mL/kg/h for >12 h
3	Increase in creatinine >300% of previous trough *or* Creatinine >4 mg/dL (>2.5 mg/dL in neonates) *or* Renal replacement therapy *or* Patients <18 years: eGFR to <35 mL/min/1.73 M^2	<0.3 mL/kg/h for ≥24 h *or* Anuria for >12 h

If there is a discrepancy between the stage of AKI as determined by serum creatinine and that determined by urine output, the patient is staged according to the worst (highest) stage. Results of the Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology (AWARE) study demonstrated that utilizing both urine output or serum creatinine captured more cases of AKI in critically ill children and young adults. The mortality rate was higher in patients who developed low urine output alone.

When evaluating AKI, it is important to remember that a rise in the serum creatinine is a late indicator of renal injury. With an abrupt change in renal clearance, the creatinine concentration will be changing until a new steady state is achieved. The estimated GFR based on the creatinine level will lag behind the actual GFR during acute deterioration of kidney function or later during recovery from AKI. Thus, it is important to realize that kidney function is worse or better than suggested by the serum creatinine for any given

A rise in the serum creatinine is a late indicator of renal injury.

In children, a relatively small increment in serum creatinine can represent a significant decline in renal function.

determination while the creatinine concentration is in a state of flux. Monitoring the rate of rise or fall of creatinine may give the clinician a better sense of their estimate of kidney function. As a corollary to the above, the GFR of an anuric patient is zero no matter what the creatinine level may be. Patients with "non-oliguric" AKI produce urine but fail to concentrate waste products in the urine.

31.3 Early Biomarkers of Acute Kidney Injury

The introduction of early therapy could potentially have a great impact on the outcome of patients with AKI. As indicated above, creatinine is a late indicator of renal injury. The identification of biomarkers in the urine or blood that may reflect very early perturbations of renal function has been the focus of much research. The ideal biomarker should be an easily measurable molecule from a convenient body fluid. Identification of early kidney dysfunction could potentially allow clinicians to investigate underlying physiologic disturbances, which, if corrected in a timely fashion, might limit further renal injury. Biomarkers that hold promise as early indicators of kidney injury (i.e., whose levels may rise prior to changes in serum creatinine) include kidney injury molecule 1 (KIM-1), L-type fatty acid binding protein (L-FABP), neutrophil gelatinase-associated lipocalin (NGAL), sodium/hydrogen exchanger isoform 3 (NHE3), cytokines (IL-6, IL-8, IL-18), urinary cysteine-rich protein 61 (Cyr61), urinary actin, urinary glutathione-S-transferases (GSTs), and cystatin C. Discovery of novel biomarkers has been complicated in the pediatric patient population by age-related variations, particularly in neonates given the increasing maturation of the tubules and improvement of GFR during the first 2 years of life. Urinary concentrations of KIM-1, NGAL, and IL-8 were found to be higher in older children. By implementation of proteomics in clinical medicine, the repertoire of urinary and plasma biomarkers to predict post cardiopulmonary bypass renal injury has enhanced significantly over the past decades. Urinary and plasma NGAL levels at 2 h after cardiac surgery had very high specificity, sensitivity, and positive predictive value for detecting AKI in children. In the Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI) pediatric cohort, children with elevated plasma IL-8 levels prior to cardiac surgery exhibited higher risk of stage II AKI. In another study, IL-18, L-FABP, and NGAL peaked within the first 6 h postoperatively before any change in serum creatinine occurred. It is very likely that future research will identify not one but a unique subset of urinary/plasma biomarkers to predict not only risk of AKI but the degree and etiology of AKI in children.

31.4 Epidemiology

In a recent study, more than 25% of children admitted to an intensive care unit (ICU) were reported to develop AKI using KDIGO criteria. Severe AKI (KDIGO stage 2 or 3) occurred in 12%, and 1.5% required renal replacement therapy. With the evolution of pediatric intensive care and the treatment of more complex and serious conditions in children, the major causes of AKI have changed over time. In a study of 227 children with AKI ranging in age from birth to 15 years who were referred to a tertiary care center for potential dialysis between 1984 and 1991, the hemolytic uremic syndrome accounted for 45% of all cases, and AKI developing after cardiac surgery accounted for an

additional 27% including 50% of cases in children less than a year of age. However, in subsequent decades, the majority of children developing AKI have an underlying comorbid condition, and the events inciting AKI in hospitalized children are often multifactorial. Primary renal disease is responsible for only about 7% of AKI in children, and hemolytic uremic syndrome is responsible for only 1%. Sepsis accounts for up to 35% of all AKI in children, surgical correction of congenital cardiac disease with cardiopulmonary bypass up to 40% (up to 60% in neonates), exposure to nephrotoxic medications 16%, and hematological-oncological conditions 19%. AKI is slightly more common in males. Moreover, neonates in the first 30 days of life are disproportionately affected, accounting for 20–24% of all cases of AKI in children. Congenital heart disease is the most common cause of AKI in neonates, ischemic insults in children under 5 years of age, and nephrotoxic agents in older children.

Most children developing acute renal failure have an underlying extrarenal comorbid condition.

Ischemic insults are the most common cause of AKI in children under 5 years of age, while nephrotoxic agents are the most common cause in older children.

31.5 Causes of Acute Kidney Injury

31.5.1 Classification

AKI may result from decreased perfusion of the kidneys, from injury to the renal parenchyma, or from obstruction of urine flow and is accordingly classified as pre-renal, renal (intrinsic), or post-renal (obstructive). In adults, 40–80% of cases of AKI are pre-renal, 10–50% are intrinsic, and less than 10% are post-renal.

31.5.2 Pre-renal Acute Kidney Injury

Pre-renal AKI is the response of the intact kidney to decreased renal perfusion secondary to diminished effective arterial filling (including volume depletion) leading to compensatory systemic and renal mechanisms to conserve salt and water. In the face of decreased renal perfusion, intrarenal autoregulation of blood flow appropriately attempts to preserve glomerular filtration. Local factors involved in this autoregulation include intrinsic myogenic responses of the glomerular arterioles, vasodilatory prostaglandins, endothelin, nitric oxide, serotonin, and tubulo-glomerular feedback. Glomerular filtration pressure is maintained by dilatation of afferent arterioles and constriction of efferent arterioles. Systemic responses include increased sympathetic nervous system activity, activation of the renin-angiotensin-aldosterone axis, and release of vasopressors such as vasopressin and endothelin. Conditions leading to the pre-renal state include volume depletion from dehydration, hemorrhage, increased insensible losses in the case of burns, third spacing of fluids postoperatively, nephrotic syndrome, liver failure, or capillary leak in sepsis, as well as diminished cardiac output resulting from cardiac systolic dysfunction or tamponade (Table 31.2). Prompt recognition and correction of the underlying cause of the pre-renal state can reverse the metabolic consequences and prevent the progression to intrinsic renal injury. The pre-renal state is itself a risk factor for the development of acute tubular necrosis. Severe, uncorrected hypoperfusion of the kidney below the limits of renal autoregulation, or the addition of nephrotoxic agents (aminoglycosides, radiographic contrast, amphotericin), or the use of agents that disrupt renal autoregulation (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, loop diuretics, mannitol) in the face of a pre-renal state, can lead to intrinsic AKI in the form of acute tubular necrosis.

The pre-renal state is reversible if recognized and treated promptly.

Table 31.2 Examples of pre-renal, intrinsic, and post-renal causes of acute kidney injury

Pre-renal	Intrinsic	Post-renal
Burns Cardiac tamponade Capillary leak Cardiac dysfunction Dehydration Diabetes insipidus Hemorrhage Liver failure Nephrotic syndrome Salt wasting nephropathy Sepsis (low cardiac output, vasoactive hormones) Third space loss (postoperative, inflammation, etc.)	Acute tubular necrosis Associated with coagulopathy (renal artery/vein thrombosis, DIC) Cirrhotic liver failure Glomerulonephritis Hemolytic uremic syndrome Hypoxia/ischemia Infiltrating tumor (bilateral) Interstitial nephritis Nephrotoxins (aminoglycosides, amphotericin B, calcineurin inhibitors, NSAIDS, etc.) Pyelonephritis Radiocontrast material Rhabdomyolysis Sepsis (ischemia) Tumor lysis syndrome Vasculitis	Bladder outlet obstruction (posterior urethral valves, tumor, urethral stone, etc.) Bilateral ureteral obstruction (ureteropelvic junction obstruction, ureterovesical junction obstruction, retroperitoneal fibrosis, tumor, etc.) Neurogenic bladder, non-neurogenic neurogenic bladder, urinary retention due to medications Obstruction of a solitary kidney

DIC disseminated intravascular coagulation, *NSAIDS* nonsteroidal anti-inflammatory drugs

31.5.3 Intrinsic Acute Kidney Injury

Intrinsic AKI can result from primary glomerular, interstitial, or vascular disease or from acute tubular necrosis (Table 31.2).

31.5.4 Acute Tubular Necrosis

Acute tubular necrosis is most commonly the result of ischemic or nephrotoxic insults.

Acute tubular necrosis accounts for approximately 45% of hospital-acquired AKI, with approximately 50% of these cases resulting from ischemic insults and 35% from exposure to nephrotoxins. The etiology of acute tubular necrosis in hospitalized patients is often multifactorial. Most research on the pathophysiology of AKI has focused on ischemic and nephrotoxin-related intrinsic renal injury. Direct endothelial and epithelial damage results in the activation of a complex molecular cascade that is directed at limiting the amount of renal injury.

31.5.5 Ischemic Renal Injury

Tubular injury results in the impaired ability to conserve sodium, giving rise to the elevated fractional excretion of sodium that is characteristic of acute tubular necrosis.

Acute ischemia may result in intrinsic renal injury secondary to a decreased glomerular filtration rate from intense renal vasoconstriction leading to diminished filtration pressure or from changes in glomerular permeability. Vascular congestion and decreased blood flow are found in the outer medulla. Injury to endothelial cells results in their swelling and expression of adhesion molecules which results in margination and activation of neutrophils, subsequently causing obstruction and stasis of vascular flow. This process likely worsens the pre-

existing hypoxia faced by the tubular segments in this zone and may explain, in part, the differential response of the various nephron segments to ischemic injury. Large-scale necrosis is unusual. In animal models, the S3 segment of the outer stripe of the medulla is the region most susceptible to injury, most likely due to reduction in the already sluggish blood flow following ischemia. These factors can lead to necrosis and apoptosis of renal tubular cells with subsequent sloughing of viable, injured, and dead cells into the tubular lumen. This process results in dilatation of tubules, transmission of increased back pressure to the glomerulus, and further impairment of filtration. In addition, there is loss of tubular integrity allowing "back leak" of significant amounts of filtrate through disrupted regions of tubular epithelium into the interstitium. This "back leak" further diminishes clearance and contributes to interstitial inflammation. Hypoxia induces loss of cell polarity and is associated with translocation of the basolateral Na^+/K^+-ATPase into the cytoplasm and even to the apical membrane. As a result of this, there is decreased reabsorption of Na^+, and the fractional excretion of Na^+ is increased. This increased fractional excretion of sodium is a clinically useful marker of intrinsic renal injury. The increased delivery of solute to the macula densa in the distal nephron can induce vasoconstriction of the afferent arteriole further decreasing GFR through tubulo-glomerular feedback. Hypoxic injury also leads to increased inducible nitric oxide synthase (iNOS) expression and increased NO release. In combination with an increase in oxygen radicals, this increased NO production can lead to the formation of peroxynitrite that is capable of causing further tubular cell damage.

31.5.6 Sepsis-Associated Intrinsic Kidney Injury

The pathophysiology of sepsis-associated AKI is incompletely understood, but it is clearly not simply due to renal ischemia. The release of vasoactive mediators appears to contribute to sepsis-associated AKI. However, the exact mechanism is not clearly elucidated with experimental research providing mixed and conflicting results. Severe renal vasoconstriction has been demonstrated in some animal models, while vasodilatation with increased renal blood flow has been observed in others. Shunting of renal blood flow through changes in the renal microcirculation appears to be involved. Inflammatory mediators such as cytokines, chemokines, complement factors, and lipopolysaccharides have direct toxic effects on tubular cells as well as recruiting inflammatory cells to the kidney. Only minor focal tubular changes are found on biopsy specimens.

Adults with AKI associated with sepsis are more likely to require mechanical ventilation and have a higher mortality rate than patients with AKI in the absence of sepsis. This may in part be due to overly aggressive fluid resuscitation in septic shock leading to increased interstitial volume and noncardiogenic pulmonary edema. Similarly, children with AKI as part of multiple organ failure have lower mortality rates if they are started on continuous renal replacement therapy at a lower percentage fluid overload.

31.5.7 Solid Organ and Hematopoietic Cell Transplantation

AKI was reported to occur within the first postoperative week in 67% of children receiving a heart, lung, liver, or multiorgan transplant and in 36% after the first postoperative week. The highest incidence occurred among children receiving a lung or multiorgan transplant.

AKI is a common complication of hematopoietic cell transplantation (HCT). In a retrospective analysis of 1057 pediatric patients, the incidence of stage 3 AKI and requirement for renal replacement therapy based on 100 days cumulative data were 25.0% ± 1.3% and 7.6% ± 0.8%, respectively. Age, year of transplantation, donor type, sinusoidal obstruction syndrome (SOS), and acute graft-versus-host disease (GVHD) were independent risk factors for stages 1 through 3 AKI.

31.5.8 Nephrotoxins

Nephrotoxins act through several mechanisms including direct toxicity to renal tubular epithelial cells, alterations in cell membranes, induction of vasoconstriction and medullary ischemia, and interference with autoregulation. Some of the nephrotoxic agents commonly encountered in the ICU setting include nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics, calcineurin inhibitors, intravascular radiocontrast agents, myoglobin from rhabdomyolysis, and amphotericin. The concept of a "triple whammy" is introduced in which combinations of diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitors (ACEI), and/or angiotensin receptor antagonists (ARB) contribute to nephrotoxicity by causing hemodynamic changes via their inhibition of prostaglandin and renin-angiotensin systems at the glomerular level.

Nephrotoxic agents commonly used in the intensive care setting include nonsteroidal anti-inflammatory drugs, aminoglycoside antibiotics, amphotericin B, calcineurin inhibitors, and radiocontrast agents.

In hospitalized patients, the combination of vancomycin and piperacillin-tazobactam causes more AKI than vancomycin and cefepime. Any one of these agents might cause AKI by itself. However, the risk of AKI is much greater, even at lower therapeutic doses, when an underlying risk factor is present in the patient, such as a pre-renal state or preexisting renal injury. Avoidance of the offending agent is essential to preventing acute renal injury in the at-risk patient. Likewise, if these nephrotoxic medications are necessary, close monitoring of drug levels is essential to lessen the potential for renal injury. Utilization of a computerized AKI monitoring program called Nephrotoxic Injury Negated by Just-in-time Action (NINJA) to flag noncritically ill hospitalized children exposed to three or more nephrotoxic medications simultaneously or an intravenous aminoglycoside for 3 or more consecutive days has resulted in a 64% decrease in AKI rate.

31.5.9 Tumor Lysis Syndrome

Children with malignancies with very large tumor burdens are at risk for the development of tumor lysis syndrome (see ▶ Chap. 39). This syndrome can occur following the release of cellular metabolites from tumor breakdown, either spontaneously or following treatment with chemotherapeutic agents, and consists of AKI developing as a result of tubular obstruction from precipitation of uric acid and calcium phosphate in the lumens. Lymphomas and leukemias are the most commonly implicated tumors. Preparation with vigorous hydration and xanthine oxidase inhibition with allopurinol may help decrease the risk of developing AKI. Urinary alkalinization can help increase uric acid solubility; however, its routine use has recently been discouraged because of the risk of increasing the likelihood of calcium phosphate precipitation. In addition, in settings of high risk for developing renal failure due to either tumor or patient factors, rasburicase, a recombinant form of the enzyme urate oxidase, can be used to achieve marked decrease in serum uric acid levels

so that attention can be focused on prevention of calcium phosphate precipitation. In the face of high serum phosphate levels, serum calcium may be quite low. Aggressive correction of hypocalcemia should be avoided in the absence of symptoms to avoid precipitation of calcium phosphate.

31.6 Primary Renal Disorders

31.6.1 Hemolytic Uremic Syndrome

The hemolytic uremic syndrome in children is usually preceded by hemorrhagic colitis and is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and AKI.

The hemolytic uremic syndrome (HUS) has become a proportionally less important cause of AKI in children over time due to the relative increase in extrarenal causes. HUS is manifested by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. In children, HUS is most frequently due to endothelial injury from Shiga-like toxin elaborated by enterohemorrhagic *Escherichia coli* (*E. coli*), in particular *E. coli* O157:H7. The onset of HUS is typically preceded by an episode of hemorrhagic colitis marked by abdominal cramping, bloody diarrhea, tenesmus, and vomiting with little or no fever. The colitis is induced by ingestion of foods or fluids contaminated by *E. coli* O157:H7 and generally lasts from 5 to 10 days. Most infections resolve at this point without sequelae. However, approximately 5% of such infections will progress to develop HUS, manifested by the sudden onset of pallor, oliguria or anuria, macroscopic hematuria, edema, and hypertension. Laboratory evaluation demonstrates a microangiopathic hemolytic anemia with fragmented red blood cells on a peripheral blood smear, thrombocytopenia, leukocytosis, elevated BUN, and creatinine. Hematuria, proteinuria, pyuria, and casts are seen on urinalysis. HUS mainly affects children between 6 months and 4 years of age with a peak incidence between 1 and 2 years of age. The kidneys are most affected, but any organ system can be involved. Treatment of typical diarrhea-associated HUS is supportive and may involve renal replacement therapy. Poor prognostic features include a marked leukocytosis at onset, prolonged anuria, prolonged diarrhea, colonic gangrene, rectal prolapse, central nervous system involvement, male gender, hypocomplementemia, and severe hypertension. The mortality rate for the typical diarrhea-associated form is less than 5%. About 5–10% of patients will have permanent renal injury. Hypocomplementemia, absence of a diarrheal prodrome, family history of HUS, or prominent CNS involvement should raise the possibility of an atypical hereditary form of HUS often associated with a deficiency of a complement regulatory protein such as factor H. These forms have a much worse prognosis but may respond to treatment with plasma exchange and eculizumab, a humanized monoclonal antibody that blocks terminal complement components C5a and the membrane attack complex (C5b-9).

31.6.2 Glomerulonephritis

A kidney biopsy is usually needed to make a definitive diagnosis and to guide therapy in cases of suspected glomerulonephritis.

Any of the glomerulonephritides may present as AKI in children. While there is a wide spectrum of severity for many of these, all can present with an acute, aggressive, rapidly progressive course. Hematuria, proteinuria, azotemia, hypertension, and edema are the hallmarks of nephritis. Specific etiologies include acute post streptococcal glomerulonephritis, IgA nephropathy, the nephritis of Henoch-Schonlein purpura, membranoproliferative glomerulonephritis, lupus nephritis, granulomatosis with polyangiitis (Wegener's granulomatosis), polyarteritis nodosa, and anti-glomerular basement membrane

disease with or without pulmonary involvement, among others. Recognition of nephritis as the cause of AKI is important because renal biopsy will be essential to confirm the diagnosis and to guide therapy—therapy that will be very different from that for other causes of AKI.

31.6.3 Interstitial Nephritis

Interstitial nephritis should be considered in patients with AKI in which a likely etiology cannot otherwise be easily determined. Critically ill patients with AKI will often be on a variety of medications with the potential to cause interstitial nephritis. Clues to this etiology include rash, peripheral eosinophilia, and eosinophiluria. However, these findings are often lacking, thus requiring a high index of suspicion. Renal biopsy can establish the diagnosis definitively, although many of these patients in the ICU are often too ill to undergo this procedure. Management involves removing the offending agent if it can be identified, with or without the administration of corticosteroids.

31.6.4 Post-renal Acute Kidney Injury

Urinary tract obstruction should always be included in the differential diagnosis of AKI and may be screened for with an ultrasound of the kidneys, ureters, and bladder.

Post-renal kidney failure is due to obstruction of the urinary tract. It involves blockage of the bladder outlet or bilateral ureteral obstruction. However, if there is only a single functioning kidney, unilateral obstruction can lead to AKI as well. Potential causes of bladder outlet obstruction in children include posterior urethral valves in males, ureteroceles, tumors, lodging of a stone or clot in the urethra, Eagle-Barrett (prune belly) syndrome, neurogenic bladder, non-neurogenic neurogenic bladder, or obstructed bladder catheter. Bilateral ureteral obstruction may be due to tumors, stones or clots, ureteropelvic or ureterovesical junction obstruction, or obstruction of a solitary kidney. While many of the congenital causes of obstruction will have underlying chronic renal failure, they may present even in older children as acute on chronic renal failure. While post-renal etiologies are uncommon causes of AKI in children, they should always be included in the differential diagnosis and screened for with ultrasound of the kidneys, ureters, and bladder (▶ Table 31.2).

31.7 Manifestations and Evaluation

AKI is often, although not always, heralded by a decrease in urine output. Oliguria in adults and older children is defined as a urine output <400 mL/day. In infants and younger children, oliguria is considered present when the urine output is <0.5–1.0 mL/kg/h. Anuria is the complete absence of urine output. Depending on the nature and severity of the inciting insult, AKI may present suddenly or insidiously. In the hospital setting, especially in the face of nephrotoxic agents or with close monitoring following a hypotensive or hypoxemic episode, acute renal dysfunction may first be detected chemically with alterations in BUN or serum creatinine, electrolyte disturbances, or discrepant fluid balance. With impaired clearance of nitrogenous wastes, BUN and creatinine levels will rise with or without accompanying oliguria. On the other hand, decreased urine output may occur prior to increases in serum biomarkers of kidney dysfunction (see definition of AKI above). Thus, both serum markers of renal function and urine output in the child at risk must be monitored closely for the early detection of AKI to allow for potential interventions to

prevent progression. The diminished clearance and tubular dysfunction may result in elevations of serum potassium, phosphorous, and uric acid. The inability to clear organic acids, secrete hydrogen ions, and regenerate bicarbonate leads to metabolic acidosis. Sodium and water retention will lead to edema and hypertension. Hypocalcemia is frequently encountered. The urinalysis in acute tubular necrosis will often demonstrate isosthenuria (inability to concentrate or dilute the urine), proteinuria, hematuria, and glycosuria with muddy brown casts and renal tubular epithelial cells on microscopy. However, bland urine can still be consistent with significant renal failure. The urinalysis in cases of acute glomerulonephritis may reveal hematuria, proteinuria, and red blood cell casts. The presence of white cells indicates inflammation but not necessarily infection of the urinary tract.

The fractional excretion of sodium is a useful measurement for differentiating the pre-renal state from intrinsic renal failure.

The evaluation of serum and urine creatinine, sodium, and osmolality can help distinguish pre-renal from intrinsic kidney injury (▶ Table 31.3). Intact tubules in the face of actual or effective decreased renal perfusion, that is, a pre-renal state, will avidly retain sodium and water in an attempt to maintain intravascular volume. As a result, the concentration of sodium in the urine will be low, the urine osmolality will be high, and the fraction of filtered sodium (FE_{Na}) excreted in the urine will be low. In the presence of hypoxic, ischemic, or nephrotoxic tubular injury on the other hand, the ability to regulate salt and water homeostasis is impaired and the amount of sodium in the urine will be high, the urine cannot be concentrated, and the FE_{Na} will be high. Because of the immaturity of tubular function, different cutoff values for differentiating pre-renal from intrinsic AKI must be used for term and premature infants. In the presence of diuretics, the FE_{Na} may be falsely elevated, rendering the test nondiagnostic. Some have advocated use of the fractional excretion of urea (FE_{UN}) for its ability to discern pre-renal from intrinsic renal disease in the presence of diuretics when the FE_{Na} was nondiagnostic. FE_{UN} <35% is considered compatible with the pre-renal state. However, certain caveats exist. Early in the course of glomerulonephritis or in contrast nephropathy, the FE_{Na} may be quite low despite adequate or more than adequate intravascular volume. In addition, intrarenal vasoconstriction due to endothelin and other agents in sepsis can lead to pre-renal urinary indices despite adequate to increased intravascular volume, cardiac output, and blood pressure. Thus, not all renal hypoperfusion is due to hypovolemia (■ Table 31.3).

The fractional excretion of urea can be used to differentiate pre-renal from intrinsic renal injury when the FE_{Na} is altered by diuretic use.

Interstitial nephritis may be manifested by an otherwise unexplained rise in creatinine in patients on medications that may incite an allergic reaction within the renal interstitium. Eosinophilia may or may not be present in the peripheral blood. The examination of the urine for eosinophils using the Hansel stain may be useful in this setting, although the absence of urinary eosinophils does not rule out the presence of interstitial nephritis. In other settings, such as in

■ **Table 31.3** Some useful renal failure indices for distinguishing pre-renal from intrinsic renal failure

	Neonate (>32 weeks gestation)		Older children	
	Pre-renal	**Intrinsic**	**Pre-renal**	**Intrinsic**
Urine osmolarity	>350 mosm/kg	<350 mosm/kg	>400 mosm/kg	<400 mosm/kg
Urine Na	<30 meq/L	>60 meq/L	<10 meq/L	>50 meq/L
FE_{Na}	<2.5	>3	<1.0	>2
FE_{UN}			≤35%	>50%

the hemolytic uremic syndrome or some instances of glomerulonephritis, patients may present with the abrupt development of oliguria, edema, and macrohematuria. A history of a preceding diarrheal illness, especially if it was bloody, should put the hemolytic uremic syndrome high on the differential diagnosis. The finding of hematuria, proteinuria, and red blood cell casts on urinalysis, with hypertension, and elevated serum creatinine points toward glomerulonephritis as a likely cause of acute renal failure. Alterations in mental status, seizures, or cerebrovascular accidents can result from rapid severe elevations in blood pressure. Congestive heart failure with pulmonary edema may result from fluid overload, and life-threatening arrhythmias may occur in the face of hyperkalemia, acidosis, and/or hypocalcemia. Disease processes such as nephrotic syndrome, cirrhotic liver failure, or heart failure may lead to pre-renal or, if sufficiently severe, intrinsic kidney injury secondary to inadequate renal perfusion. In these, as well as in other settings of renal insufficiency, agents that alter renal perfusion, such as nonsteroidal anti-inflammatory agents in particular, may precipitate intrinsic kidney injury in an otherwise compensated pre-renal situation. In the case of many patients with cancer, no one etiology of AKI can be identified, and it is likely that multiple factors such as episodes of mild hypotension, the use of nephrotoxic agents, the presence of an inflammatory state, and/or relatively mild dehydration precipitate renal shutdown. The abrupt onset of anuria suggests acute obstruction of the urinary tract which may occur from a stone or clot blocking the urethra or an obstructed catheter draining the bladder. Other more chronic processes causing urinary tract obstruction, such as tumor impingement on the urinary tract or congenital urinary tract malformations, may not present with complete anuria but rather with abdominal distension and/or the presence of a suprapubic or flank mass. Medications that may lead to urinary retention as a side effect should be considered as a possible etiology.

Lupus serologies, complement levels, antistreptococcal antibodies, antineutrophil cytoplasmic antibodies, and anti-glomerular basement membrane antibodies may diagnose suspected cases of glomerulonephritis.

All critically ill infants and children are at risk for developing AKI and should have serum electrolytes, calcium, phosphorous, BUN, and creatinine monitored at regular intervals to detect early changes in renal function. This is especially true of any patient receiving nephrotoxic agents or who has preexisting renal insufficiency. Patients presenting with edema, hypertension, gross hematuria, and proteinuria will often have glomerulonephritis as the underlying cause of intrinsic AKI. In addition to the above described laboratory studies and a complete blood count, initial evaluation in these patients will also require evaluation of serum complement levels and antinuclear antibody titers. If the history or physical exam is suggestive of glomerulonephritis, and if the presentation is particularly severe, or if an etiology is not apparent after the initial evaluation, anti-double-stranded DNA antibodies, anti-streptolysin O or streptozyme titers, serum antineutrophil cytoplasmic antibodies, and anti-glomerular basement membrane antibodies should be obtained. Insidious onset of AKI can occur in cases of acute interstitial nephritis that may be due to immune reactions to medications and viral infections or may be idiopathic. A catheterized urine specimen for culture should be always obtained in the febrile child with kidney injury.

Patients undergoing chemotherapy for malignancies should have serum phosphorous and uric acid levels carefully monitored in the face of large tumor burdens. In the presence of crush injuries or viral myositis such as can be seen with influenza infections or ischemic injury to limbs, serum creatine kinase levels and urinary myoglobin should be determined. Rhabdomyolysis should be suspected if the urine is positive for heme in the absence of red blood cells on microscopic examination of the urine.

Renal biopsy may be necessary to make a definitive pathologic diagnosis and to guide therapy if the etiology of AKI is unclear, in cases of suspected acute tubular necrosis with a prolonged course, or if glomerulonephritis is suspected.

An attempt should be made to categorize the cause of the AKI as pre-renal, intrinsic, or obstructive. The history should inquire about recent decreased intake or vomiting; abnormal losses from polyuria, diarrhea, wounds, or drains; and recent exposure to nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, chemotherapeutic agents, intravenous radiocontrast, or aminoglycosides. A history of edema, gross hematuria, hypertension, or changes in urine output as well as a past history of nephrolithiasis, chronic renal disease, and cardiac, hepatic, oncologic, or collagen vascular disease should be sought. If known, the baseline value of serum creatinine should be sought since AKI can complicate chronic renal disease. The family history should be reviewed for clues to the cause of kidney injury.

The history and exam may suggest dehydration or hypoperfusion. Low blood pressure, tachycardia, blood and urine chemistries revealing an elevated serum urea to creatinine ratio, and a very low fractional excretion of sodium (FE_{Na}) suggest that dehydration or underperfusion is present.

An obstructive cause of AKI should always be considered and ruled out with an ultrasound examination of the kidneys, ureters, and bladder, assessing for hydronephrosis, masses, and/or stones. Visualization of the ureters suggests vesicoureteral reflux or obstruction below the level of the ureteropelvic junction. Bladder wall thickening suggests outlet obstruction as might be seen with neurogenic bladder, posterior urethral valves in males, prostatic tumors, or an obstructing urethral stone or clot. Depending on the findings, further imaging by computerized axial tomography, magnetic resonance imaging, cystourethrogram, or radioisotope nuclear studies may be indicated.

31.8 Management

The first step in managing AKI is to assure adequate intravascular hydration.

Central venous pressure monitoring may be helpful in guiding fluid resuscitation in the severely dehydrated, oliguric patient.

The management of AKI requires recognition and careful correction of disturbances of fluid, electrolyte, and acid-base balance, as well as attention to nutritional needs. When the urine output is first noted to diminish or the serum creatinine is noted to rise, a cause should be quickly sought and corrected if possible. Shock, if present, should be treated promptly. A bladder catheter should be placed to monitor urine output accurately. In cases of obvious underlying dehydration, or if the cause of the AKI is unknown but the patient is not clinically fluid overloaded, a fluid challenge should be given. Recent studies have warned of the risk of hyperchloremic acidosis, decreased renal perfusion, and hypertension with the overly aggressive use of normal saline for resuscitation, and utilization of balanced solutions such as Plasma-Lyte or lactated Ringer have been recommended. More studies are needed regarding best practice for the choice of resuscitation fluids for volume restoration in critically ill patients. If dehydration is severe, multiple fluid boluses may be required to restore perfusion with close monitoring of the exam to avoid fluid overload if urine output is not restored. If the etiology or fluid status is less clear, smaller, more frequent fluid boluses may be appropriate. Early goal-directed therapy is recommended, and central venous monitoring may be helpful in these situations. If urine output is restored and renal function quickly returns to baseline, any remaining fluid deficit should be replaced, and sufficient fluid should be provided for maintenance and to replace any ongoing losses. Avoidance of marked fluid overhydration is important for preventing subsequent complications.

Despite being associated with total body fluid overload, nephrotic syndrome, congestive heart failure, and cirrhotic liver disease all have decreased effective arterial filling and present a significant pre-renal state at risk for progression to acute tubular necrosis.

Patients with nephrotic syndrome, congestive heart failure, or liver failure may present with edema in the face of renal underperfusion. The FE_{Na} will be low in these patients, indicating the decreased effective arterial filling and the physiologic mechanisms elicited to conserve salt and water despite the total body water overload. Diuretics are important in the management of patients with heart failure and can improve cardiac function and renal perfusion. In the case of the nephrotic patient, infusion of 0.5–1 g/kg of 25% albumin over 2–4 h in conjunction with a loop diuretic may improve renal perfusion. Acute kidney injury associated with liver failure may be secondary to pre-renal conditions, acute tubular necrosis, or hepatorenal syndrome. Hypovolemia should be corrected with fluid challenges to assure adequate intravascular filling. In addition, diuretics should be discontinued, and any potential for an infection should be assessed and treated accordingly. Optimization of cardiac output and augmentation of mean arterial pressure with vasoactive agent infusions (norepinephrine, vasopressin analogs, octreotide), augmentation of intravascular volume with albumin, as well as reduction of abdominal compartment pressure with paracentesis may improve renal perfusion in these patients. Mortality is high in the patient with hepatorenal syndrome. Dialysis is a bridging therapy until a liver transplant, the definitive treatment, can be performed. As in all pre-renal states, nephrotoxic agents should be avoided to prevent progression to intrinsic kidney injury. Renal function, by means of BUN and creatinine or cystatin C if available, along with electrolytes, should be monitored closely.

31.8.1 Fluid Management

Patients who present with oligoanuria and who are not clinically volume overloaded should receive fluid resuscitation and their volume status and urine output response reassessed. Several fluid challenges may be required with close attention paid to not overhydrate the patient in the face of anuria. Central venous pressure monitoring may be helpful in this situation. Adequate fluid resuscitation is the one factor repeatedly found to be most effective in preventing or ameliorating the severity of AKI in a variety of settings. Patients who are adequately hydrated can be given a loop diuretic intravenously in an attempt to induce urine flow. In the face of severe kidney injury, a fairly large dose or a continuous infusion of furosemide should be considered. However, it must be realized that the place of diuretics in the management of AKI is controversial (see below). In the absence of a response, repeat doses are unlikely to be successful and may in fact be harmful.

Insensible fluid losses are replaced with electrolyte-free intravenous fluids at about 25% of daily maintenance requirements.

Patients who remain oligoanuric despite adequate resuscitation should have their fluid input curtailed to cover insensible losses plus any ongoing losses. Insensible fluid losses consist of water losses from the respiratory tract and evaporation (not sweat) from the skin. Losses from normal stool in older children are negligible. Evaporative losses are higher in infants given their greater relative body surface area. Insensible fluid losses are essentially electrolyte-free and should be replaced with electrolyte-free water (D_5W, $D_{10}W$, etc.). Daily replacement rate for insensible fluid losses is estimated at 20–30 mL/100 kcal expended/day (about 25–30% of maintenance fluid requirements) or 300–500 mL/M^2/day. Rates can be adjusted up for persistent fever or burns leading to higher evaporative losses or down for highly humidified inhaled air that may decrease respiratory losses in ventilated patients. All other losses over and above insensible fluid losses should be replaced. These may include diarrheal losses, any urine output, losses from drains, etc. Replacement of these fluid losses can often be initiated with D5½NS on a mL per mL basis while awaiting

the results of the electrolyte composition of the fluid in question. The electrolyte composition of the fluid being lost should guide the choice of the replacement fluid used. The electrolyte composition of ongoing fluid losses should be monitored once or twice a day initially, and the replacement fluid composition adjusted accordingly. Losses from surgical drains, thoracostomy tubes or pericardial drainage, may at times contain significant amounts of protein and may require replacement with 5% albumin or periodic supplementation with 25% albumin. In general, albumin replacement is not used for a low serum albumin level without overt losses. While fluid and electrolyte balance can often be maintained for significant periods of time in this manner in fairly stable patients, the obligatory fluid intake associated with intermittent medications and continuous infusions for many critically ill patients may preclude effective fluid restriction. Likewise, it is usually impossible to provide adequate nutrition to the severely fluid-restricted patient. Therefore, strong consideration should be given to initiating renal replacement therapy very early in the course of oliguric AKI to remove uremic toxins, to maintain fluid and electrolyte balance, and to allow for adequate nutrition. Adequate nutrition may improve overall function and immune status, thereby decreasing the risk of infection and promoting the healing of injured tubules as well as other affected organs.

31.8.2 Diuretics

Theoretically, diuretics could prevent or ameliorate AKI by converting oliguric to polyuric kidney injury by flushing out casts and debris causing tubular obstruction, decreasing oxygen demand in the loop of Henle, and increasing medullary blood flow. However, furosemide was associated with an increased risk of developing AKI in critically ill children. Thus, compelling evidence of benefit deriving from the use of diuretics to prevent AKI is lacking. The use of a high dose of a loop diuretics may lead to diuresis in the oliguric, volume-resuscitated patient early in the course of AKI, making the fluid and electrolyte management of those patients easier. However, this most likely reflects less severe renal injury compared to those that do not respond rather than a determinant of outcome. In the responsive patient, diuretics may have a role in controlling or avoiding fluid overload. In the absence of a diuretic response, repeated doses of loop diuretics are not recommended and may be harmful. In a study of 338 adults with established AKI requiring renal replacement therapy, administration of high-dose furosemide had no impact on mortality or recovery of renal function.

31.8.3 Vasopressors

Norepinephrine is preferred to dopamine to support blood pressure in septic patients with AKI. Norepinephrine can increase systemic blood pressure and renal blood flow leading to improved urine output and glomerular filtration. Vasopressin can also increase systemic blood pressure and improve urine output. Vasopressin can be used in patients who do not respond to norepinephrine.

The ability of the methylxanthines, aminophylline, and theophylline to induce intrarenal vasodilation through adenosine receptor antagonism has led to their use in states of renal compromise. A randomized, controlled trial in asphyxiated neonates demonstrated improved renal function in the group receiving theophylline.

There is no compelling evidence to support the use of renal dose dopamine infusions in patients with AKI.

Although low dose infusions (0.5–2 mcg/kg/min) of dopamine leads to increased renal blood flow, natriuresis, and diuresis in laboratory animals and healthy humans, low-dose "reno-protective" dopamine has no role in the management of patients with AKI. In a prospective, randomized study of 328 critically ill adult patients with evidence of systemic inflammatory response syndrome and signs of early renal dysfunction, infusion of dopamine at 2 mcg/kg/min made no difference in the increase in serum creatinine, the number of patients requiring renal replacement therapy, the length of hospitalization, or the mortality compared to the control group. In addition, there are potential side effects of dopamine including decreased respiratory drive, increased myocardial oxygen consumption, predisposition to gut ischemia, hypokalemia, and hypophosphatemia, as well as impairment of immune function. Thus, there is no compelling evidence to support the use of renal dose dopamine infusions in patients with AKI, with some evidence suggesting that it may be deleterious.

Fenoldopam mesylate is a dopamine type 1 receptor agonist that has similar effects to dopamine. There is no convincing data supporting the benefits of using fenoldopam to prevent AKI, and its use is not recommended.

Atrial natriuretic peptide (ANP) has a natriuretic, diuretic, and vasodilator effect. However, in a systemic review and meta-analysis of 19 studies investigating the use of ANP for the prevention and treatment of AKI, ANP was found to not be beneficial in preventing oliguric AKI. Although the subset analysis comparing low-dose versus high-dose ANP suggested some benefit, there was no significant improvement in the requirement of renal replacement therapy or in the mortality rate in patients receiving ANP.

31.8.4 Correction of Electrolyte Imbalances

Hyponatremia is a common finding in AKI. Unless there is an obvious source of sodium loss, hyponatremia in this setting is most commonly due to dilution from water retention. Total body sodium is usually in excess as well. Therefore, management requires fluid restriction. Trying to correct low serum sodium with sodium containing fluids will lead to volume and salt overload.

Hyperkalemia is another commonly observed electrolyte disorder in AKI due to the decreased ability to excrete potassium. High levels can lead to cardiac conduction anomalies and arrhythmias. Acidemia causes a shift of potassium from within cells to the extracellular fluid. Correction of acidemia may therefore improve hyperkalemia by driving potassium intracellularly. All sources of exogenous potassium should be discontinued, if possible. Antibiotics, for example, some penicillins, can be a significant source of potassium in the context of kidney injury, and alternatives should be considered. In addition to sodium bicarbonate, sodium polystyrene sulfonate, glucose and insulin, and β_2-adrenergic agonists such as albuterol can be used to reduce hyperkalemia. Intravenous administration of calcium salts (calcium gluconate or chloride), while not reducing the level of hyperkalemia, will reverse some of the negative metabolic consequences of hyperkalemia, such as cardiac conduction defects and arrythmias.

Hypocalcemia can lead to tetany and conduction defects. Symptomatic hypocalcemia can be treated similarly to hyperkalemia with calcium infusions. Correction of coexisting hypomagnesemia may need to be addressed before hypocalcemia can be corrected. It is also important to recognize that correct-

ing hypocalcemia in the face of significant hyperphosphatemia can lead to precipitation of calcium phosphate into tissues resulting in organ dysfunction. As in the example of tumor lysis syndrome in which severe hyperphosphatemia is a common occurrence, correcting the serum calcium level can lead to precipitation of calcium phosphate crystals in renal tubules obstructing the flow of filtrate and resulting in or worsening of AKI. Thus, correction of hypocalcemia in these situations should be judicious and based more on symptoms than an absolute level of calcium.

Metabolic acidosis can arise from the inability to excrete acid and the retention of organic acids. Acidemia can depress myocardial function along with more generalized cell function. Treatment consists of administering sodium bicarbonate with the goal of raising the blood pH to approximately 7.2. Base correction of acidemia can decrease the ionized calcium and may precipitate tetany if hypocalcemia is also present.

Correction of electrolytes and acid-base disturbances can lead to salt and volume overload and exacerbate hypocalcemia in the face of aggressive bicarbonate use. Sodium overload can occur with repeated use of sodium polystyrene sulfonate. Complex disturbances of electrolytes in the face of AKI will often require institution of renal replacement therapy.

31.8.5 Indications for Renal Replacement Therapy

Medical management of AKI often precludes the provision of adequate nutritional support in which case renal replacement therapy should be instituted.

The early institution of renal replacement therapy may improve survival rates in children with AKI.

The indications for initiating renal replacement therapy (RRT) are failure of medical management to control volume overload, electrolyte imbalances, metabolic acidosis, and uremia. In addition, certain endogenous and exogenous toxins are amenable to removal by dialysis. It is important to realize that while electrolyte disturbances, acidemia, and volume overload can sometimes be controlled by medical management alone, provision of adequate nutrition is critical for recovery of patients with organ failure. In this setting, adequate calories often cannot be provided within the restrictions necessary to maintain fluid balance, thus necessitating the initiation of RRT. Children with fluid overload more than 10% at RRT initiation have more than three times greater risk of mortality in comparison to children with low or no fluid overload. Initiation of RRT should be considered in the child with 10–20% fluid overload since mortality increases dramatically with increasing fluid overload.

The choices of renal replacement modalities include peritoneal dialysis, intermittent hemodialysis, and continuous veno-venous hemofiltration and its various permutations (see ▶ Chap. 32). The modality of renal replacement therapy depends on the indication, the clinical status of the patient, and the experience of the individual center with the different modalities. For rapid removal of excess volume, correction of hyperkalemia, or removal of poisons or endogenous toxic metabolites, intermittent hemodialysis will usually be a better option than the slower modalities of peritoneal dialysis or continuous hemofiltration. On the other hand, in the patient with significant cardiovascular instability, slow continuous fluid and solute removal as occurs with continuous hemofiltration or peritoneal dialysis are more likely to be tolerated than the rapid changes that occur with intermittent hemodialysis. It would not be advisable to introduce an unfamiliar modality in the midst of the care of a critically ill patient without the prior training of all staff involved, development of treatment and monitoring protocols, and familiarity with the functioning and troubleshooting of the equipment.

31.8.6 Peritoneal Dialysis

Peritoneal dialysis is a conceptually straightforward technique that provides slow continuous dialysis.

Peritoneal dialysis provides slow continuous dialysis through the infusion of dialysate into the peritoneal space via a peritoneal dialysis catheter, allowing the fluid to dwell. This dwell allows for the osmotic movement of fluid and the diffusion of solutes and metabolites into the dialysate. The dialysate is then drained, and the cycle is repeated as often as needed to maintain fluid and electrolyte balance. The technique is relatively straightforward, and access can be obtained fairly easily, even at the bedside if necessary, although surgical placement is preferred. Peritoneal dialysis can be performed by means of an automated cycler or manually, as may be necessary in very small infants. Potential problems include leakage of dialysate and risk of infection, mechanical interference with exchanges, compromise of pulmonary status by increased abdominal volume impinging on diaphragmatic excursions, and leakage of dialysate into the thorax. Peritoneal dialysis may not provide sufficient clearance in very large or hypercatabolic patients. However, in the absence of adequate vascular access or availability of other modalities, peritoneal dialysis may provide an important treatment option. Routine peritoneal dialysis catheter placement at the time of congenital heart surgery and the initiation of peritoneal dialysis as needed resulted in shorter time to negative fluid balance, earlier extubation, improved inotrope scores, and fewer electrolyte imbalances.

31.8.7 Hemodialysis

Hemodialysis is the modality of choice for rapid correction of severe electrolyte disturbances, such as hyperkalemia, or the rapid removal of toxic metabolites such as occurs in certain inborn errors of metabolism.

Intermittent hemodialysis provides rapid and efficient correction of electrolyte and fluid disturbances and management of uremia. Trained experienced staff is required. Hemodialysis can be performed even in infants; however, adequate vascular access with a large-bore dialysis catheter is essential. Hypotension during initiation may occur when blood is initially drawn into a relatively large extracorporeal circuit primed with only crystalloid. Other risks include line infection, dialysis disequilibrium from too rapid removal of urea, cramping and hypotension related to fluid and solute removal and shifts, bleeding from unintentional line disconnections or over-anticoagulation, clotting from inadequate anticoagulation, electrolyte imbalances from improper dialysate composition, and dialyzer membrane reactions.

31.8.8 Continuous Renal Replacement Therapies

Continuous veno-venous hemofiltration can often provide slow, continuous fluid removal and correction of electrolyte and acid-base disturbances even in hemodynamically unstable patients.

A common limitation of the use of intermittent hemodialysis is preexisting hypotension in the unstable patient or induction of hypotension on initiating the treatment which precludes adequate fluid removal. This inability to remove fluid impairs the ability to compensate for the fluid input required to provide nutrition, vasoactive infusions, and medications. In these situations, continuous modalities are best suited because they allow for slow fluid and solute removal with or without exchange of plasma water. Dialysate can be run countercurrent to improve efficiency of fluid and solute removal. Regarding the provision of nutrition, continuous therapies can remove as much as 20% of amino acids administered with total parenteral nutrition and lead to negative nitrogen balance. This requires an increase in protein supplementation. Veno-venous methods have replaced arteriovenous setups because of the better control of blood flow and ultrafiltration. This modality, however, requires specially trained staff and more complex and expensive equipment. Central vascular

access is required with large-bore catheters for this modality, as with intermittent dialysis. With the exception of the disequilibrium syndrome observed with intermittent hemodialysis, complications are similar between the two modalities.

31.8.9 Pharmacologic Considerations in Acute Kidney Injury

Acute kidney injury impacts the renal clearance of many drugs and their volume of distribution necessitating the modification of the doses and dosing intervals.

Many medications are eliminated from the body by the kidneys. When glomerular filtration and tubular function are impaired, these drugs may accumulate to toxic levels. As renal function declines, it is necessary to modify medication dosages to avoid toxicity. In addition, the volume of distribution of many drugs is altered as a result of AKI. It is important to realize that although some of the accumulating drugs may have direct toxic effects on the kidneys (aminoglycosides, amphotericin B), others have their doses modified to avoid toxicity to other organ systems (high levels of ampicillin causing seizures). Dose recommendations for drugs cleared by the kidneys are based on the estimated residual renal function. In the presence of AKI, the level of renal function is often changing until a new steady state is achieved. With the current commonly available clinical means of measuring renal function, often only crude estimates can be made and must be constantly modified as new information arises. This introduces the risk of under- or overdosing medications. The introduction of renal replacement therapy further complicates matters since clearance of a drug may differ between different modalities and even with different permutations of the same modality. Dosing guidelines for children are available from several sources.

31.9 Prevention of Acute Kidney Injury

The single most important measure for preventing many forms of AKI is assuring adequate intravascular volume and perfusion.

In the patient at high risk for development of AKI, every effort should be made to modify risk factors early to try to prevent or at least mitigate the course of AKI. This includes fluid resuscitation to optimize volume status for the patient with actual or relative intravascular volume depletion and stopping or avoiding nephrotoxic agents where possible. Normal saline or balanced salt solutions are the first-line therapy to restore organ perfusion instituting early goal-directed therapy with attention to central venous pressure, oxygenation, and arterial pressure. If large volumes of normal saline are used for resuscitation, attention should be directed to acid-base status and avoiding hyperchloremia which itself can cause kidney injury through renal vasoconstriction. In this case, intravenous fluids should be switched to a balanced salt solution. Depending on the situation, colloid infusion may be indicated in which case albumin is the preferred agent. Attempts should be made to avoid overhydration, and a vasopressor agent such as norepinephrine should be added for the patient in whom fluid therapy is inadequate to restore organ perfusion. Once adequate volume status and perfusion are restored, intravenous fluids should be cut back, and if needed, diuretic or renal replacement therapy initiated to try to achieve euvolemia since overhydration is a risk factor for mortality. Mortality in children with 10–20% fluid overload was found to be 40% while it was 60% in those with >20% fluid overload.

On the other hand, the patient at risk for AKI who presents with fluid overload will be managed differently. The patient with glomerulonephritis and oligoanuria will likely require fluid and salt restriction and the underlying kidney disease addressed. The patient with nephrotic syndrome may benefit from

intravenous 25% albumin infusion with or without a loop diuretic to restore intravascular oncotic pressure and improve renal perfusion and urine flow. Patients with congestive heart failure may require diuretics and have their underlying cardiac dysfunction addressed.

Medications should be reviewed with the aim of discontinuing and avoiding any nephrotoxic agents as the clinical situation persists. The patient with intravascular volume depletion should not receive diuretics until the volume status is improved. Angiotensin converting enzyme inhibitors and angiotensin receptor blocking agents should be held. Nonsteroidal anti-inflammatory drugs should be discontinued. Alternative non-nephrotoxic antimicrobial therapy should be considered with every attempt made to avoid aminoglycosides and vancomycin, especially in combination with piperacillin-tazobactam, among others. Once-daily dosing of aminoglycosides should be used in situations in which other alternatives are not practical. Antibiotic blood levels should be monitored closely to guide dosing. Lipid formulations of amphotericin B should be used preferentially. The need for IV radiocontrast for imaging should be carefully considered. Pre- and post-hydration with normal saline or a bicarbonate solution should be provided if a radiocontrast agent must be given. The lowest dose of an iso- or low-osmolality agent that will address the clinical question should be used. Recent studies have not confirmed a benefit of N-acetylcysteine in preventing contrast-induced nephropathy. While any one insult by itself may not lead to the development of AKI under normal conditions, combinations of nephrotoxic agents especially in the setting of an underperfused/ischemic kidney increase the risk considerably. Hyperglycemia is a common occurrence in critically ill patients, and rigorous control of blood sugar has been found to decrease the risk of AKI by up to 34%. However, tight blood glucose control must be weighed against the risk of inducing hypoglycemia.

Given the molecular and cellular mechanisms involved in the development of AKI, many investigators have attempted interventions to prevent or ameliorate AKI and decrease the associated mortality. Unfortunately, while many animal models have demonstrated great promise for particular interventions, human clinical trials have been generally disappointing. For example, antitumor necrosis factor-α antibodies, platelet-activating factor antagonists, nitric oxide synthase inhibitors, atrial natriuretic peptide analogs, recombinant tissue factor pathway inhibitor, antithrombin III, insulin-like growth factor-1, activated protein C, selenium infusion, and human growth hormone have not matched their performance in animal models when attempted in human clinical trials. Given the complexity of the molecular and cellular pathways involved in the development of AKI, it is possible that individual agents alone may not modulate morbidity and mortality, but combinations of agents may prove to be beneficial.

31.10 Effect of Renal Failure on Other Diseases

The presence of underlying renal disease or even the presence of risk factors for the development of AKI can complicate the management of other diseases. For example, the patient with a pre-renal state due to hypotension from sepsis is at increased risk of developing AKI with the administration of an aminoglycoside. The patient with chronic renal disease requiring imaging studies with intravenous contrast administration for evaluation of an unrelated problem is at high risk of developing acute on chronic kidney injury. In each example, the presence of underlying renal disease or risk factors for the development of

AKI may influence diagnostic or therapeutic measures required to manage other disease processes.

The development of AKI is an independent risk factor for death in critically ill children. AKI increases the risk of morbidity and death in patients with underlying conditions such as multiple organ dysfunction syndrome, hematopoietic stem cell transplantation, trauma, and extracorporeal membrane oxygenation use when compared with patients with the same severity of disease but without renal failure. Across the spectrum of kidney injury, AKI by itself can induce dysfunction in distant organs such as the brain, heart, liver, and lung through aberrant "AKI-distant organ cross talk." These effects are mediated by fluid overload, electrolyte and acid-base disturbances, immune dysfunction, production of inflammatory mediators, endothelial injury with changes in vascular permeability, cellular apoptosis, and oxidative stress. Consequences include neurologic impairment, myocardial injury, alterations in hepatic protein synthesis and drug metabolism, pulmonary edema, and the need for and prolongation of mechanical ventilation.

In the opposite direction, disordered organ cross talk can induce AKI through a variety of mechanism. Examples include the development of AKI that can be observed with the treatment of respiratory failure with mechanical ventilation, the cardiorenal and hepatorenal syndromes, and the effects of alterations of the gut microbiome.

31.11 Prognosis

In the prospective, multicenter AWARE study of the epidemiology of AKI in children and young adults, 11% of the patients admitted to a pediatric ICU who developed severe AKI (KDIGO stage 2 or 3) died compared to 2.5% without severe AKI. Severe AKI was associated with use of renal replacement therapy, mechanical ventilation, and longer stay in the PICU. The degree of fluid overload at the initiation of continuous RRT had a strong influence on survival with 40% mortality in those with 10–20% fluid overload and 60% mortality in those with >20% fluid overload. Solid organ and hematopoietic cell transplantation were associated with higher risk of severe kidney injury. The need for RRT predicted a threefold higher risk of death. In addition to being an important risk factor for death, patients with AKI had increased ICU and overall hospital length of stay and greater need for and longer duration of mechanical ventilation.

Survival in children with AKI and an underlying comorbid condition is significantly worse than if AKI is due to primary kidney disease.

Survival is better in children older than one year of age as compared to those less than a year of age. Patients with non-oliguric acute renal injury have better survival (74%) than those who are oliguric (60%). Survival is better if AKI is due to primary renal disease rather than systemic disease. In a study assessing survival differences associated with different RRT modalities and different causative disease processes, survival of children requiring RRT was less than 50% for those with AKI associated with bone marrow transplantation, congenital heart disease, liver transplantation, or sepsis. Fifty-five percent of patients who continued to require RRT at discharge had primary renal disease as the cause of AKI. There are few pediatric studies addressing renal recovery after AKI. Among children with AKI who required RRT, only 27% achieved an estimated glomerular filtration rate >90 mL/min/1.73 M^2 within 1 month of discharge. Long-term rates of hypertension (20%), proteinuria (20%), and eGFR <90 mL/min/1.73 M^2 (14%) in children following AKI have been reported.

31.12 Summary

Acute kidney injury is a relatively common condition affecting critically ill patients in the intensive care unit. When it develops as a complication of another disease process, survival is adversely affected. AKI may develop insidiously, and renal function should be monitored closely in "at-risk" patients. Risk factors for the development of AKI should be assessed and monitored. Risk factors, in particular volume status, should be addressed aggressively at the earliest possible time to try to prevent or ameliorate the course of AKI. Nephrotoxic agents should be avoided if allowed by the clinical situation, especially in "at-risk" patients. The consequences of AKI should be managed meticulously. Institution of RRT should be instituted early to manage uremia and fluid, electrolyte, and acid-base imbalances and to allow for the provision of adequate nutrition. Long-term monitoring of survivors of AKI is essential, especially among those requiring RRT, given the high incidence of hypertension, proteinuria, and chronic kidney disease. With the improvement in our understanding of the mechanisms leading to the development and persistence of AKI, treatment may move from primarily supportive to more actively therapeutic in the near future.

Review Questions

1. A 3-year-old boy, who is neutropenic secondary to chemotherapy for acute lymphoblastic leukemia spiked a fever of 39 °C. His baseline serum creatinine level is 0.4 mg/dL. At the time of his fever, he was mildly hypotensive for a brief period but responded promptly to a single saline bolus. He is being treated with cefepime and gentamicin. Gentamicin levels have been within the therapeutic range. Eight hours after the febrile hypotensive episode, his creatinine is still 0.4 mg/dL, and his urine output is 1 mL/kg/h. Given this information, you conclude that
   A. Given the mild nature of the hypotension, the risk of developing acute kidney injury is low.
   B. He has not sustained any renal injury.
   C. The normal gentamicin level is reassuring and that the dose is safe and does not require further monitoring.
   D. The serum creatinine level should be monitored closely for several more days.
   E. The urine output indicates normal renal function.

2. A 10-year-old girl (height 140 cm, weight 35 kg) had open heart surgery 7 days ago. Her serum creatinine has peaked at 1.2 mg/dL for the past 3 days. Her estimated GFR is approximately
   A. 120 mL/min/1.73 M^2
   B. 90 mL/min/1.73 M^2
   C. 70 mL/min/1.73 M^2
   D. 50 mL/min/1.73 M^2
   E. 30 mL/min/1.73 M^2

3. Which of the following children with acute kidney injury has the best prognosis?
   A. A neonate with congenital heart disease
   B. A 2-year-old male with typical, postdiarrheal hemolytic uremic syndrome
   C. A 5-year-old male who has received a hematopoietic cell transplant
   D. A 10-year-old female with sepsis
   E. A 17-year-old male with Hodgkin lymphoma

4. A 5-year-old male who has recently required resection of infarcted bowel has developed gram-negative sepsis and respiratory failure. His blood pressure is 58/30 mm Hg requiring substantial fluid resuscitation. His blood urea nitrogen level is 70 mg/dL, serum creatinine level is 3.0 mg/dL, and his urine output is 0.3 mL/kg/h. After assuring adequate intravascular volume status, the best treatment option would be to
   A. Administer a nitric oxide synthase inhibitor.
   B. Administer repeated doses of a loop diuretic to improve urine flow.
   C. Initiate an infusion of adenosine.
   D. Initiate a low-dose dopamine infusion to improve urine flow.
   E. Initiate a norepinephrine infusion to support blood pressure.

5. In the patient described in question 4, oliguric kidney injury persists with significantly mismatched fluid balance with worsening edema, worsening ventilatory status, and marginal systemic blood pressures despite the use of vasopressor support and fluid boluses. The serum sodium level is 130 mmol/L, and the serum potassium level is 6.2 mmol/L. Of the following options, the best choice for this patient would be
   A. Continuous arteriovenous hemofiltration.
   B. Continued medical management with sodium polystyrene sulfonate, diuretics, and sodium bicarbonate.
   C. Continuous veno-venous hemofiltration.
   D. Intermittent hemodialysis.
   E. Peritoneal dialysis.

6. A 10-year-old with hemophagocytic lymphohistiocytosis received a hematopoietic cell transplant. He is admitted to the intensive care unit after developing sepsis. He is intubated and on multiple vasoactive infusions. He is oliguric and his serum creatinine has doubled in 24 h. His weight is 30 kg and he is edematous on physical exam. His dry weight is 25 kg. His fluids are restricted to 400 mL/M^2. Which of the following would be the best next step to decrease the risk of mortality of this patient?
   A. Administration of a high-dose loop diuretic
   B. Continuous renal replacement therapy
   C. Intermittent hemodialysis
   D. Low-dose dopamine infusion
   E. Peritoneal dialysis

Answers

1. D
2. D
3. B
4. E
5. C
6. B

Suggested Reading

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Renal Replacement Therapies

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Contents

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Learning Objectives

- To recognize the main indications for renal replacement therapy
- To identify the various modalities of renal replacement therapy
- To understand the fundamental working principles of each modality of renal replacement therapy
- To understand the advantages and the associated risks of each individual modality of renal replacement therapy
- To appreciate the appropriate access needed for renal replacement therapy
- To understand the various forms of continuous renal replacement therapy and their appropriate application to clinical situations

32.1 Introduction

Renal replacement therapies (RRT) have been used for more than three decades in children. The primary indications for RRT include acute kidney injury (AKI), inborn errors of metabolism, and intoxications (Table 32.1). This book chapter will describe the modalities used throughout the world and address the risk and benefits of each one. Additionally, insight will be offered regarding the optimal modality of therapy based on the underlying indication for RRT. The modalities of RRT described in this chapter include peritoneal dialysis (PD), continual flow peritoneal dialysis (CFPD), hemodialysis (HD), sustained low-efficiency dialysis (SLED), and continuous renal replacement therapy (CRRT).

32.2 Peritoneal Dialysis (PD)

Peritoneal dialysis (PD) is considered a standard throughout the world for AKI therapy. PD has been used for more than three decades in children. The equipment required for PD includes peritoneal access for PD delivery, dialysate solutions, and tubing.

32.2.1 PD Access

PD access can be cuffed or non-cuffed. Cuffed access can classically be single cuffed or double cuffed, with either a straight configuration or a swan neck configuration with a curl at the end. These catheters are typically placed by surgical colleagues with the openings of the catheter positioned in the pelvis

Table 32.1 Indications for acute renal replacement therapy

A. Acute kidney injury
a. Fluid overload with pulmonary edema and/or respiratory failure
b. Uremia with encephalopathy or bleeding
c. Severe metabolic derangements: hyperkalemia, acidosis, hyperphosphatemia
d. Nutritional support
B. Inborn errors of metabolism
C. Intoxications

area for maximum flow. An omentectomy is commonly performed in this setting in order to avoid adherence of the omentum to the peritoneal dialysis catheter.

Acute access is typically non-cuffed. There are many companies that manufacture catheters that can be placed using the Seldinger technique at the bedside. These catheters are usually placed below the umbilicus and can be positioned in the left or right lower quadrant of the peritoneum. These catheters can be placed by physical exam or by ultrasound guidance based on the experience of the individual placing the catheter. In other parts of the world, sterile catheters including chest tubes, feeding catheters, as well as intravenous catheters have been used for acute peritoneal dialysis.

32.2.2 Solutions for PD

Solutions for peritoneal dialysis in the United States are lactate based. Outside of the United States, options for PD solutions include bicarbonate-based solutions. The disadvantage of a lactate-based solution primarily occurs in the patient with compromised hepatic metabolism in which an acidosis and/or an elevated lactate level may occur as the liver is not able to sufficiently metabolize the lactate to bicarbonate. Outside of the United States, bag technology has allowed for improvement in the delivery of bicarbonate-based solutions at the bedside. Classically, the components of PD solutions are mildly hyponatremic (Na of 132 mEq/dL) and contain no potassium or phosphorous. Additional electrolytes can be added based on the individual needs of the patient.

32.2.3 PD Tubing

Peritoneal dialysis can be performed using either a manual or an automated system. The automated system (e.g., Fresenius and Baxter) allows for the delivery of PD solutions via a machine. Automated systems may be complicated by a large "dead space" in the PD tubing, thereby affecting dialysis efficiency. Manual PD systems such as the Pedialyte (Gesco Utah Medical) can be used easily at the bedside. These systems utilize the buretrol infusion and drainage system so accurate inputs and outputs can be determined. The advantage of this system is that there is only 6 mL of dead space as opposed to the other PD systems which may have dead space three to four times larger.

32.2.4 Heating Units in PD

Heaters are incorporated into the automated systems. In contrast, there is no heater in the manual system. Therefore, it is critical to assure that hypothermia does not occur at the time of PD.

32.2.5 Initiation of PD

At the initiation of PD, it is not unusual that the fluid coming out of the peritoneal cavity may be full of fibrin or blood. Therefore, the standard practice is to place 250–500 units of heparin per liter into the PD solution. This will allow for diminished fibrin formation without resulting in systemic heparinization.

32.2.6 Antibiotics in PD

Antibiotics may be given intraperitoneally for peritonitis and be maintained systemically if necessary. In a patient with no residual renal function, the only loss of antibiotics will occur either via hepatic metabolism or by loss via dialysis. In those patients with renal function, the urine output will also affect the clearance of antibiotics. Classically, intraperitoneal antibiotics such as cephalosporins, vancomycin, and aminoglycosides are used for local installation into the abdomen for peritonitis. In patients who are anuric, a single dose of antibiotics may be given intravenously, and the same antibiotic may be placed intraperitoneally to maintain adequate levels in both the peritoneum and systemically in the body.

In patients who are anuric and undergoing peritoneal dialysis, a single dose of antibiotics may be given intravenously, and the same antibiotic may be placed intraperitoneally to maintain adequate levels in both the peritoneum and systemically in the body.

32.2.7 Complications of PD

Complications of PD include peritoneal leak at the site of the catheter, peritonitis, impairment of diaphragmatic movement decreasing ventilation, and drainage or movement of the peritoneal dialysis fluid from the peritoneum into the thoracic cavity. Additionally, over time, PD will result in a negative nitrogen balance, removing albumin as part of the solute clearance. Attention to these potential risk factors may minimize complications and improve outcomes. In the face of a leak at the site of the catheter, it is helpful to decrease the volume of the PD solution and to consider "gluing" the exit site of the catheter access. In the case of peritonitis, appropriate antimicrobials need to be given intraperitoneally. If fungal peritonitis occurs, optimal therapy requires removal of the PD catheter and the establishment of alternative forms of dialysis. The effect of PD upon diaphragmatic excursion as well as respiratory function is important to understand. As the abdomen fills with dialysate, the diaphragm will move upward, decreasing total pulmonary and functional residual capacity and diminishing respiratory integrity. Therefore, close monitoring of respiratory function is essential during PD therapy. Finally, there may be an efflux of peritoneal solution from the peritoneal cavity into the pleural space. If a pleural effusion develops in a child receiving PD, a simultaneous tap of the pleural effusion and an analysis of PD solution instilled in the abdomen should be performed. A similar composition in both (i.e., glucose) suggests efflux of dialysis fluid into the pleural cavity. In the face of such a hydrothorax, discontinuation of PD or a longer drain time should be considered to minimize the ongoing fluid collection in the thorax.

Complications of PD include peritoneal leak at the site of the catheter, peritonitis, impairment of diaphragmatic movement decreasing ventilation, and drainage or movement of the peritoneal dialysis fluid from the peritoneum into the thoracic cavity.

32.2.8 Solute Clearance in PD

Solute clearance in PD is based on the volume per pass, the components of the PD solution, as well as the number of cycles.

At the start of PD, each pass typically consists of only 10 mL/kg. However, over time (usually measured in weeks) that volume increases to 40–50 mL/kg per pass; solute clearance will improve with the larger volumes with better clearance of phosphorus, urea, and potassium. The number of cycles per day will also improve the clearance. Therefore, 12 hours per day will provide less clearance than 24 hours per day. Finally, the components of the PD solution will be important. For example, if the patient has a high potassium concentration, the PD solution should contain little to no potassium. In contrast, if the potassium level is low or decreasing, potassium may be added to the PD solution in order to minimize excess clearance.

Solute clearance in PD is based on the volume per pass, the components of the PD solution, as well as the number of cycles.

32.2.9 Ultrafiltration of PD

Ultrafiltration of PD is classically affected by the frequency of passes, by the osmolality of the solution (as measured by the dextrose content), as well as by the length of the pass. Solute clearance is best accomplished with longer passes while ultrafiltration is best attained with shorter passes in order to maintain a high osmolality. Therefore, for a patient with fluid overload, pulmonary edema, or other systemic findings of fluid excess, a high dextrose concentration such as 4.25% dextrose will be more proper to use to facilitate ultrafiltration. In contrast, in patients with normal or hypovolemia, a 1.5 or 2.5% dextrose solution may be more appropriate to use.

32.3 Continuous-Flow Peritoneal Dialysis

Advantages of continuous-flow peritoneal dialysis (CFPD) compared to standard PD include less pulmonary impact and substantially better clearance.

Continuous-flow peritoneal dialysis (CFPD) was first identified by Amerling and colleagues over a decade ago. Recent and pediatric-specific work by Nourse has identified that CFPD can be performed easily at the bedside, negating some of the problems associated with standard PD. CFPD is performed using the same solutions of PD. The difference with CFPD is that two catheters are placed in the abdomen. One is an inflow and the other is an outflow catheter. By using this technique, the patient can be loaded with 10 mL/kg of dialysate and have that fluid held in the abdomen. A continuous dialysate flow of 10 mL/kg/hour on the infusion side is then initiated, while at the same time, drainage of the PD solution occurs via the outflow catheter. Clearance can be improved by increasing the intraperitoneal infusion rate. Advantages of CFPD compared to standard PD include less pulmonary effect (less diaphragmatic changes) and substantially better clearance with CFPD.

The disadvantage of CFPD is that it requires placement of two catheters in the abdomen. In theory, a double-lumen 7 Fr, non-cuffed vascular catheter may be placed in the peritoneum, and both ports of that catheter may be used to perform CFPD. Similar to standard PD, CFPD may cause problems with amino acid losses, immunoglobulin losses, hypothermia, and electrolyte disturbances. Therefore, attention to these potential complications is essential to effective dialysis and quality outcomes.

32.4 Hemodialysis

Hemodialysis may be performed at the bedside. It requires vascular access that can be cuffed or non-cuffed as well as the equipment for hemodialysis. It may be performed as standard or high flux. The difference between these two modalities is that standard HD removes lower-molecular-weight molecules as opposed to high-flux or high-efficiency HD which results in the removal of higher-molecular-weight products.

32.4.1 Vascular Access

Data to date have suggested that in the acute setting, a cuffed or non-cuffed catheter is equally effective. However, for outpatient chronic hemodialysis, a cuffed catheter is more appropriate. The vascular access, whether cuffed or non-cuffed, is proportional to the size of the child. For example, a 10 kg child may require a 7 Fr catheter while a larger child such as a 60–70 kg child would need at least an 11 Fr catheter (see recommendations at ► www.pcrrt.com and ◘ Table 32.2).

Table 32.2 Suggested vascular access based upon size of the child

Patient size	Catheter
>30 kg	11.0 Fr dual lumen
16–30 kg	9.0 Fr dual lumen
5–15 kg	7.0 Fr dual lumen
Neonate	UVC 5.0–8.0 Fr, 5.0 Fr single lumen, or 7.0 Fr dual lumen

Adapted from Bunchman and Donckerwolcke (1994)

32.4.2 Blood Flow Rate for Hemodialysis

The blood flow rate (BFR) for HD is often started at approximately 5 mL/kg/min. This can be increased as necessary to maintain patency of the catheter as well as to minimize clotting. A contraindication of a rapid BFR is in those patients who are hyperosmolar (e.g., elevated blood urea nitrogen (BUN), sodium, or glucose concentration) and at high risk for a rapid drop in osmoles that will result in dialysis disequilibrium. Dialysis disequilibrium occurs when there is too brisk of drop in the serum osmoles of the patient potentially resulting in seizures or cerebral demyelination.

Dialysis disequilibrium occurs when there is too brisk of a drop in the serum osmoles of the patient potentially resulting in seizures or cerebral demyelination.

The classic scenario for dialysis disequilibrium occurs in a child with a sodium of 140 mmoles/L, a glucose of 100 mg/dL, and a BUN of 150 mg/dL. In standard or high-flux hemodialysis, the BUN may be cleared by two-thirds in the first 2–3 hours of dialysis. Consequently, if the BUN decreases acutely by 100 mg/dL, the osmoles would decrease by approximately 35 mOsm/L which would place the patient at risk for disequilibrium. Recall, plasma osmolality can be calculated with the formula 2 Na (mOsm/L) + (urea [mg/dL])/2.8 + (glucose [mg/dL])/18, where 2.8 and 18 are used to convert mg/dL to mOsm/L based on the molecular weight. Therefore, a lower BFR would be indicated in this situation and in any situation where there is a risk for dialysis disequilibrium. However, in most other settings, a higher BFR is reasonable.

32.4.3 Dialysate Flow Rate

The dialysate flow rate can range anywhere from 300 to as high as 800 mL/min. This is somewhat HD machine dependent. Higher dialysate flow rates, especially with a high-porosity membrane (high-flux membrane), provide greater solute clearance. In smaller children, excess solute clearance may occur, and thus, the dialysate flow rate may need to be decreased in order to have less clearance. Some children (e.g., neonates with anuria) may require dialysis 4–5 days/week due to the fact that their nutrition is liquid based. In this setting, the dialysate flow rate may need to be decreased in order to avoid hypophosphatemia.

The temperature in HD can range from 34.0 to 39.5 degrees Fahrenheit. This is important for infants particularly those having a fair amount of bedside cooling. Therefore, meticulous attention to body temperature must occur to assure that hypothermia does not occur in this setting. In those patients that are febrile, one can promote normothermia by decreasing the core temperature via the dialysis. However, the practitioner must recognize that the patient would otherwise be febrile and evaluate and treat the etiology of the hyperthermia accordingly (e.g., sepsis).

32.4.4 Extracorporeal Blood Volume in Hemodialysis

The "10% rule" suggests that extracorporeal blood volume should not exceed 10% of the total intravascular blood volume when performing hemodialysis.

In performing hemodialysis, particularly in the infant and small child, it is essential to assess the extracorporeal blood volume of the circuit relative to the patient. For example, a 10 kg infant will have an intravascular blood volume of approximately 80 mL/kg or 800 mL. Therefore, if one accepts the "10% rule" that extracorporeal blood volume should not exceed 10% of the total blood volume, it would be prudent to have no more than 80 mL of blood volume extracorporeal to the patient. If the required extracorporeal blood volume is excessive, a blood prime of the circuit at the initiation of hemodialysis may be required.

However, the use of a blood prime has two problems associated with it; the first is the component of the blood itself, and the second is the potential impact upon transplantation in the future. In an acute setting, a blood prime is less concerning for transplant issues because the focus is for survival and potential reversibility, not for transplantation. In terms of blood composition, it is important to recognize that blood blank blood has a pH of 6.4, an ionized calcium 0.02 mmoles/L, and a potassium concentration that may be as high as 40 mEq/L. Therefore, it is necessary to be aware that in the first 5–10 min of initiation of blood prime in a child with AKI, a metabolic acidosis, hypocalcemia, and/or hyperkalemia may result from the components of the blood bank blood.

32.4.5 The Standard Prescription for Hemodialysis

A standard prescription for hemodialysis in a non-acute setting is a duration of 3–4 hours with a goal rate of ultrafiltration based on the volume status of the patient as assessed by the blood pressure as well as by the physical exam. The components of the dialysate are standard with a sodium concentration of 140 mEq/L, bicarbonate of 35 mEq/dL, a calcium level that would reflect a physiologically normal value approximating 10.5 mg/dL, and a potassium concentration that may range from 2 to 5 mEq/L. Most hemodialysis solutions contain no phosphorus, but phosphorus may be added in order to avoid hypophosphatemia during dialysis. In an acute setting, HD may be performed for a shorter or longer period of time based on the needs of the patient.

Solute clearance in HD is the greatest of all the dialysis modalities and can occur with or without ultrafiltration. Electrolyte and blood chemistry values as well as the need for medications and nutrition will determine the need for solute clearance, while the daily weight and the physiological parameters of blood pressure, oxygen requirements, and heart rate will determine ultrafiltration goals. Typically, the goal is to remove the entire historical weight gain since the last HD session over a 3- to 4-hour period of time if physiological parameters allow for that. If this amount of fluid cannot be removed in this relatively short period of time, then an alternative RRT modality may be required.

32.4.6 Anticoagulation in Hemodialysis

Anticoagulation in hemodialysis is usually achieved using heparin. Heparin can be initiated with a bolus of 20 U/kg followed by an infusion of 10 U/kg/hour for the duration of HD titrating to a bedside activated clotting time (ACT) of 180–200 seconds to avoid system clotting. Although this range of dosing should have minimal risk of systemic bleeding, the child needs to be monitored for this risk.

32.5 Sustained Low-Efficiency Dialysis

Although sustained low-efficiency dialysis (SLED) has been used commonly in adults for over two decades, there is very little experience in pediatrics. There are two pediatric studies, one out of Taiwan and one out of India, demonstrating its utility in pediatrics.

SLED is a hybrid between HD and CRRT. In the United States, SLED may only be performed in the dialysis mode, but outside of the United States, it may be used with filtration or so-called SLEDF. Dialysis and filtration can both occur in the setting of SLEDF for maximum benefit of large and small molecule removal.

Sustained low-efficiency dialysis (SLED) shares many similarities with HD but differs in the duration of dialysis as well as in the dialysate flow rate.

SLED shares many similarities with HD. First, it requires the same vascular access. Next, the extracorporeal blood volume of SLED, much like HD, needs to be calculated carefully. Therefore, utilizing the "10% rule," no more than 10% of the blood volume should be extracorporeal to the patient in either modality. Presently, both a low volume system for pediatrics and adult volume systems are commercially available. Additionally, the membranes used in HD and in SLED are very similar. Finally, the blood flow rate in SLED is similar to HD as well as the dialysate constituents and temperature control.

However, the two approaches differ in the duration of dialysis as well as in the dialysate flow rate. In classic HD, dialysis will run for 3–4 hours; in contrast, it is continued for 6–12 hours in SLED. In terms of the dialysate flow rate, the standard HD dialysate flow rate is approximately 500 mL/min or 30 L/hour, while in SLED or SLEDF, the dialysate will flow at only 100 mL/min or 6 L/hour.

As described above, data regarding the use of SLED in pediatrics are limited. However, data from Taiwan and India suggest that SLED is very effective in delivering the therapies needed to address AKI. However, data to date have not established a role for the use SLED in the treatment of either inborn errors of metabolism or intoxication, but those data are being generated.

32.6 Continuous Renal Replacement Therapy (CRRT)

There are three primary forms of CRRT including continuous veno-venous hemofiltration (CVVH; convective clearance), continuous veno-venous hemodialysis (CVVHD; diffusive clearance), and continuous veno-venous hemofiltration with dialysis (also referred to as continuous veno-venous hemodiafiltration (CVVHDF)) which is a combination of convective (CVVH) and diffusive (CVVHD) clearance.

Continuous renal replacement therapy (CRRT) has been used for more than two decades in children. There are three primary forms of CRRT including continuous veno-venous hemofiltration (CVVH; convective clearance), continuous veno-venous hemodialysis (CVVHD; diffusive clearance), and continuous veno-venous hemofiltration with dialysis (also referred to as continuous veno-venous hemodiafiltration (CVVHDF)) which is a combination of convective (CVVH) and diffusive (CVVHD) clearance (Fig. 32.1).

Similar to hemodialysis, CRRT machines are marketed by only a few companies. Features common to CRRT machines include an accurate ultrafiltration monitor as well as a venous and an arterial pressure monitor. Despite the provision of an internal blood warmer, maintaining normothermia can be a challenge with the CRRT machine especially in smaller children because of the disproportionate large surface area and relatively large extracorporeal volume. The use of external warming may be necessary in some instances to maintain normothermia of the patient.

CRRT extracorporeal blood volumes can range from 60 mL up to 200 mL. This is an important issue given the "10% rule" of permissible extracorporeal blood volume. Consequently, blood priming of the extracorporeal

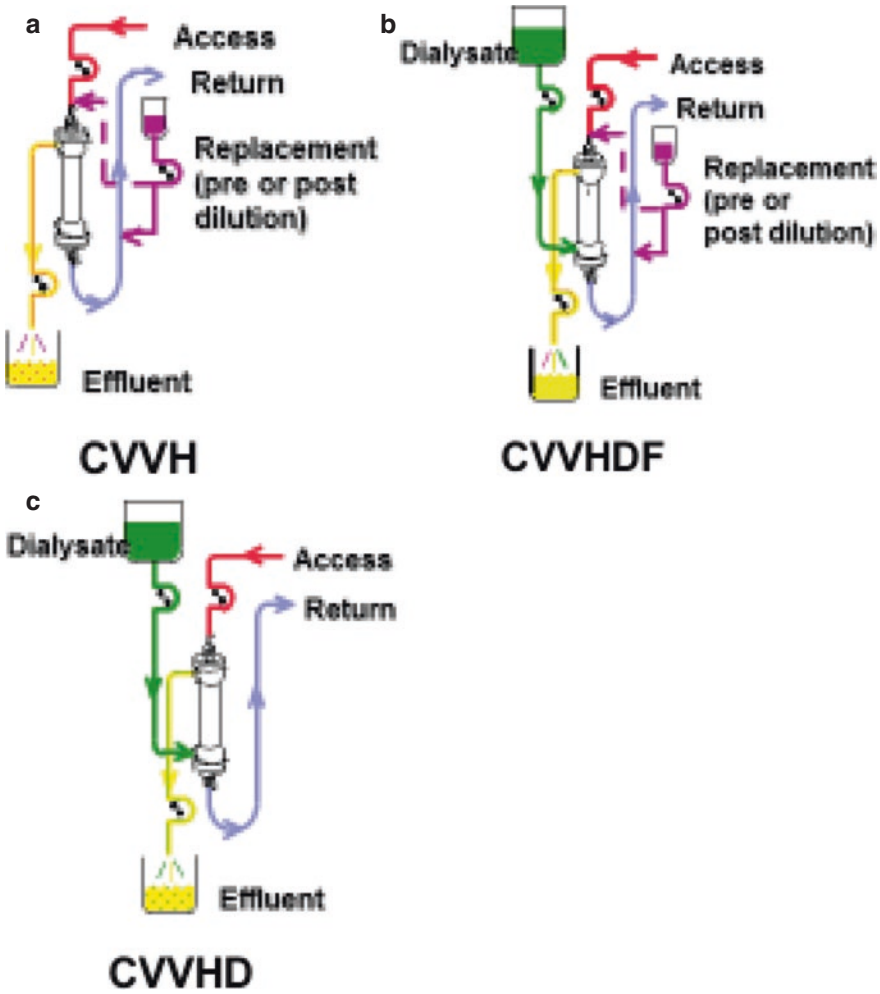


Fig. 32.1 The diagrams depict the setup and circuitry of the three modes of continuous renal replacement therapy. **a** Illustrates the setup for continuous veno-venous hemofiltration (CVVH). Blood is accessed from the patient (red) and powered through the membrane filter using a motorized blood pump. As the blood moves through the filter, the ultrafiltrate (yellow) passes through and is channeled into a collecting bag. The ultrafiltration rate must be closely monitored and adjusted based on the hemodynamic status of the patient and the fluid intake. As depicted in purple, replacement fluid is infused either pre- or post-filter. Pre-filter administration serves to dilute the blood prior to passing through the filter and thereby holds the theoretical advantage of extending filter lifetime. **b** Illustrates the setup for continuous veno-venous hemodialysis (CVVHD). In this mode, a dialysate solution (green) is run countercurrent to the blood flow, and replacement fluid is not used. **c** Illustrates the setup for continuous veno-venous hemodiafiltration (CVVHDF). As depicted in the diagram, this mode of continuous renal replacement therapy utilizes both replacement fluid and a dialysate solution

CRRT circuit is often required especially in hemodynamically compromised patients. As mentioned in the HD section, blood bank blood carries its own inherent risks of acidosis, hypocalcemia, and hyperkalemia. In addition, episodes of anaphylaxis have been reported to occur with blood priming and certain CRRT membranes as a result of the acidotic blood triggering a bradykinin reaction when it interfaces with these membranes. Although protocols to

mitigate this side effect have been established, the risk can also be obviated by the use of polysulfone membranes as these have not been associated with the bradykinin reactions.

32.6.1 Selection of CRRT Modality

The choice of CVVH, CVVHD, or CVVHDF is, in large part, a style of practice. Work by Maxvold and colleagues identified that similar prescriptions in convection (CVVH) or diffusion (CVVHD) result in similar, if not identical, clearance of small-molecular-weight solutes such as urea or citrate. However, large-molecular-weight solutes (e.g., vancomycin) have a preferential clearance in the convective mode.

Similar prescriptions in convection (CVVH) or diffusion (CVVHD) result in similar clearance of small-molecular-weight solutes such as urea or citrate. However, large-molecular-weight solutes (e.g., vancomycin) have a preferential clearance in the convective mode.

Thus, the decision of convection versus diffusion should not be based solely on style of practice but should also incorporate the sieving coefficient of the toxin or the medication to be removed. For example, vancomycin is approximately 1500 KDa and 75% protein bound. The sieving coefficient of vancomycin with CVVH is approximately 0.85, while with CVVHD, it approximates 0.75. The sieving coefficient is the ratio of the concentration of solutes in the ultrafiltrate to that of plasma. A sieving coefficient of one reflects complete permeability, while a sieving coefficient of zero reflects complete impermeability. Thus, vancomycin is more effectively cleared with CVVH rather than CVVHD.

A classic CRRT prescription includes a blood flow rate of approximately 5 mL/kg/min (although this is vascular access dependent) and a dialysate or replacement fluid rate approximating 40 mL/kg/hour or 2000–2500 mL/1.7 M^2 corrected for body surface area per hour. The amount of fluid removal is based on the hemodynamic status of the patient. Although there is a tendency to try to remove as much fluid as possible in patients on CRRT, the amount and rate of fluid removal should be based on the hemodynamics of the child including the blood pressure and heart rate.

32.6.2 Anticoagulation in CRRT

Anticoagulation in CRRT can be accomplished using heparin, citrate, or, in some programs, prostacyclin. Examples of anticoagulation protocols can be found at the website (► www.pcrrt.com). Brophy and colleagues reported that performing CRRT without anticoagulation results in a circuit life of only 24 hours. Although their study demonstrated no difference in circuit life between citrate and heparin anticoagulation, more recent data published by Zaoral and others have suggested that citrate use is associated with longer circuit life than heparin.

Prostacyclin has also been suggested as an alternate anticoagulant for CRRT in those settings when heparin and citrate cannot be used.

Prostacyclin has also been suggested as an alternate anticoagulant for CRRT in those settings when heparin and citrate cannot be used, when they may be associated with increased risk, or when they may be ineffective, particularly in patients with an underlying coagulopathy and hepatic insufficiency. The risk of bleeding with heparin therapy is exacerbated in children with hepatic failure. The risk of citrate toxicity, with its inherent potential for metabolic, calcium, and acid-base imbalances, is increased in the setting of liver dysfunction as citrate metabolism is largely dependent on liver function. Citrate toxicity, or "lock" as it has been termed, occurs when the level of citrate exceeds

the metabolism and clearance of citrate. The characteristic laboratory findings are a rising patient total calcium with a stable or even decreasing patient ionized calcium. In theory, this has the potential to impact muscle and cardiac metabolism. The treatment for citrate lock is to decrease the citrate infusion rate as well as to increase the replacement fluid and/or dialysate rate. Prostacyclin therapy is also not without risk as it can result in vasodilatation and a risk of hypotension and/or ventilation perfusion mismatching.

32.6.3 CRRT Use with Extracorporeal Membrane Oxygenation (ECMO)

CRRT use in conjunction with extracorporeal membrane oxygenation (ECMO) is now quite common. In this setting, CRRT may be utilized in one of two ways. In the first approach, a hemofilter is simply placed "in line" to perform slow continuous ultrafiltration (SCUF). This approach will allow for fluid clearance but will have little to no effect upon solute clearance. It may be accomplished by attaching the arterial limb to the post-ECMO pump stopcock and the venous limb to the pre-pump bladder. However, because the resistance of the oxygenator of the ECMO circuit is greater than the resistance of the hemofiltration membrane, adjustments may be needed to prevent shunting of blood away from the oxygenator. The second approach involves the use of a standard CRRT machine "in line" with the ECMO circuit. The advantage of this approach is that it has the added benefit of solute clearance as well as more accurate ultrafiltration control.

32.7 Nutrition Losses in Renal Replacement Therapy

Classically, PD and CFPD result in large losses of protein, amino acids, and albumin in the setting of chronic dialysis. Hemodialysis and SLED have a higher risk of mineral and vitamin losses. CRRT has been found to remove approximately one-third of the amino acids delivered as well as trace elements. Therefore, attention to nutrition and maximization of nutrition delivery in these patients are important.

32.8 Medication Clearance

Medication clearance is affected by the dialysis prescription, the protein binding, the molecular weight, and the distribution of the medication. In patients on CRRT, it is not unusual that vasoactive medications (e.g., epinephrine, norepinephrine, dopamine, and dobutamine) are cleared easily because they are small-molecular-weight compounds with low protein binding. Therefore, it is essential to monitor for hemodynamic compromise with the initiation of CRRT as the process may result in removal of these vasoactive medications. In particular, the proximity of the dialysis catheter to the infusion site of the vasoactive medication is important to assess. If the RRT access is in the immediate proximity of the infusion site of the vasoactive medications, the likelihood that these medications will be cleared is enhanced and the likelihood of hemodynamic compromise increased.

In comparison to CRRT, PD has less effect upon drug clearance. HD is considered the optimal therapy for drug clearance particularly in cases of

intoxication (see below). Little data exist regarding medication clearance with SLED; however, it would seem to be similar to HD, but less efficient.

32.9 Indications

As previously described, RRT can be used to treat three primary conditions including AKI, inborn errors of metabolism, and intoxications (Table 32.1). The decision of what modality to use is based, in large part, on the experience of the center and clinician as well as on the clinical condition of the patient. PD or CFPD is often utilized for the treatment of infants. Hemodynamically stable patients with minimal oxygen requirements can effectively be treated with HD or SLED. Additionally, postoperative cardiac patients frequently have a PD catheter placed in the peritoneum especially in the setting of a long cardiac pump bypass time; these infants may accumulate ascites, and the PD catheter can be used for RRT or to drain ascites. However, PD would be a suboptimal modality for patients with life-threatening hyperkalemia, severe volume overload, or intoxications that would benefit from rapid ultrafiltration or solute clearance. In those settings, intermittent HD would provide a more effective modality for rapid ultrafiltration and solute clearance. In patients with hemodynamic compromise or those who are inflamed such as hematopoietic cell transplant patients or those with sepsis, CRRT may be beneficial over other modalities of RRT. In addition, the optimal RRT modality for AKI is based on the experience of the clinician, available resources, and the experience of the bedside staff.

32.9.1 Inborn Errors of Metabolism

Picca has identified that all modalities of RRT including PD, HD, and CRRT can be used as clearance for ammonia. However, work by our group has identified that maximum clearance of ammonia can be achieved by HD. If the need of clearance is ongoing, the use of sequential HD followed by CRRT is the optimal way to address elevations of ammonia in infants with inborn errors of metabolism.

The maximum clearance of ammonia can be achieved by hemodialysis (HD), and if the need of clearance is ongoing, the use of sequential HD followed by CRRT.

Although HD is challenging to perform in small infants, with close monitoring of hemodynamics as well as meticulous thermic control, HD has been performed in patients down to 2 kg. Given that these children with inborn errors of metabolism usually have normal renal function, components of the dialysate bath must be adjusted to ensure that normal physiological concentrations of electrolytes are maintained.

32.9.2 Intoxications

Several factors must be considered in applying RRT in the treatment of a toxic ingestion. First, it is necessary to determine if the drug is primarily impacted by renal or hepatic metabolism. In the setting of hepatic or renal dysfunction, the drug itself (or the by-product of the drug) may be retained resulting in toxicity. If systemic toxicity is observed, particularly if it is impacting neurologic and/or cardiac function, then RRT is often indicated. Other issues that must be considered when determining the role for RRT include whether the drug is a short-acting or sustained-release product, as well as the volume of distribution, molecular weight,

Table 32.3 Characteristics of common drugs which may require renal replacement therapy in intoxication

Drug	Molecular weight (Da)	Volume of distribution (L/kg)	% Protein bound
Vancomycin	1500	0.2–1.25	75
Gentamicin	477	0.25–0.3	0
Lithium	6.9	0.6–0.9	0
Aspirin	138	0.17	90
Theophylline	180	0.45–0.7	60
Carbamazepine	236	0.8–1.8	78
Valproic acid	144	0.1–0.2	90
Metformin	166	0.5	0
Methotrexate	454	Acute use 0.18	50
		Chronic use 0.4–0.8	

and protein binding of the drug. Table 32.3 illustrates these characteristics for common medications that may require RRT in settings of intoxication.

In the setting of medication intoxication, a high-flux or high-efficiency HD membrane provides the largest and most effective form of medication clearance.

A high-flux or high-efficiency HD membrane provides the largest and most effective form of medication clearance.

This often requires a large membrane, a high blood flow rate, and a very high dialysate flow rate. For some medications (e.g., vancomycin), clearance is impacted by a "two-compartment" model. In these situations, after an initial clearance of the medication by a course of HD, it is not unusual for there to be a rebound in the serum level 4–6 hours after dialysis as medication in the tissues moves back to the vascular space in response to the lowered serum concentration. Therefore, and similar to the case of the inborn errors of metabolism, the use of sequential HD followed by CRRT (preferably in a convective mode) may be necessary to provide optimal and continual clearance of these medications or toxins. Also, and again similar to the situation of an inborn error of metabolism, these children may have normal renal function, and attention to the components of the dialysate bath is necessary to ensure normal physiological levels of electrolytes.

32.10 Summary

In summary, RRT is a useful therapy for many critically ill children, particularly those with AKI, those with inborn errors of metabolism, and those experiencing some forms of intoxication. It may also be useful in the setting of extracorporeal membrane oxygenation. There are several forms of RRT, and the choice of RRT modality is based on a combination of factors including the clinical state of the patient (particularly the hemodynamics), the experience of the practitioner, and local resources. Data to date have not demonstrated one modality to be superior or inferior to any other for all indications and clinical conditions. Table 32.4 compares five modalities of dialysis, including the need for anticoagulation, the dialysate or replacement flow rate, as well as the impact upon nutrition, drug clearance, and hemodynamics.

Table 32.4 Comparison of renal replacement modalities

	CRRT	SLED	Hemodialysis[a]	Peritoneal dialysis
Blood flow rate	3–5 mL/kg/min Access dependent	3–5 mL/kg/min Access dependent	3–5 mL/kg/min Access dependent	Not applicable
Dialysate flow rate	0–4 liters per hour	6 liters per hour	30–50 liters per hour	0.5–2 liters per hour
Convective flow rate	0–4 liters per hour	0	0	0
Systemic anticoagulation	Heparin or citrate	Heparin or citrate	Heparin or none	None
Thermic control	Yes	Yes	Yes	Partial
Ultrafiltration control	Yes	Yes	Yes	Partial
Dialysis solutions	Industry prepared	Online production	Online production	Industry prepared
Drug clearance	Continuous	Intermittent	Intermittent	Continuous
Nutritional clearance	Continuous	Intermittent	Intermittent	Continuous
Solute clearance[c]	2	3	1	4
Hemodynamic stability[b,c]	1	3	4	2

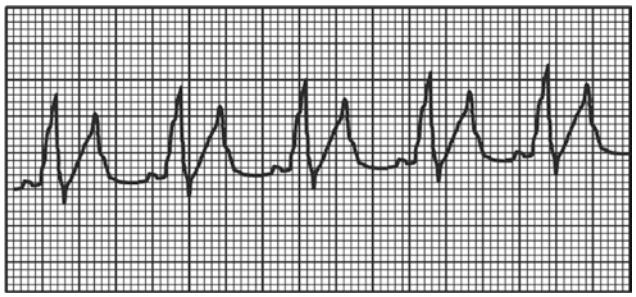
[a]Standard or high-flux intermittent hemodialysis
[b]Permits ultrafiltration with hemodynamic stability
[c]The scoring reflects the relative effectiveness of the modalities compared with each other with a "one" signifying the best and a "four" indicating the worst

Review Questions

1. Which of the following statements is correct regarding peritoneal dialysis?
   A. Increasing the dextrose concentration of the dialysate solution may enhance solute clearance but will decrease ultrafiltration.
   B. Peritoneal dialysis is the most effective dialysis modality for treating life-threatening hyperkalemia.
   C. Solute clearance of phosphorus, urea, and potassium are enhanced using larger exchange volumes approximating 50 mL/kg per pass.
   D. Ultrafiltration with peritoneal dialysis is enhanced with longer pass times.

2. A 17-year-old adolescent is transferred to the intensive care unit with severe hemolytic anemia secondary to a brown recluse spider bite. On clinical exam, he is somnolent but arousable. He is tachypneic but easily oxygenated with nasal cannula oxygen. His heart rate is 105 bpm, and his blood pressure is 129/79 mm Hg. His distal pulses are 1+. His ECG rhythm strip is depicted below. He has become severely oliguric (<0.2 mL/kg/min).
   Laboratory analysis reveals the following:
   - White blood cell count: 21,000/μL
   - Hemoglobin: 4.8 g/dL
   - Platelet count: 98,000/μL
   - Lactate dehydrogenase: 9800 U/L

- Sodium: 132 mmol/L
- Potassium: 7.8 mmol/L
- Chloride: 100 mmol/L
- Bicarbonate: 16 mmol/L
- Blood urea nitrogen: 82 mg/dL
- Creatinine: 4.1 mg/dL
- pH: 7.37
- $PaCO_2$: 27 mm Hg
- PaO_2: 116 mm Hg
- Base deficit: −8



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In addition to standard medical therapy, which of the following therapies should be implemented to provide the most effective treatment of his most immediate life-threatening problem?

A. Continuous arteriovenous hemofiltration
B. Continuous veno-venous hemofiltration
C. Hemodialysis
D. Peritoneal dialysis

3. A 4-day-old male presents with multiple organ dysfunction syndrome and encephalopathy. The infant is intubated, mechanically ventilated, and started on a dopamine infusion for pulmonary and hemodynamic stabilization. Laboratory workup reveals severe hyperammonemia (ammonia level 1285 μmol/L). The Genetics service is consulted and suspects a urea cycle defect, most likely ornithine transcarbamylase deficiency. The therapy most urgently needed to improve his chance of successful outcome includes which one of the following?

A. Hemodialysis
B. Lactulose
C. Neomycin
D. Peritoneal dialysis

4. Which of the following statements is true regarding the use of continuous renal replacement therapy in children?

A. Continuous veno-venous hemofiltration (CVVH) provides less clearance of large-molecular-weight solutes (e.g., vancomycin) than continuous veno-venous hemodialysis (CVVHD).
B. The continuous nature of fluid removal in continuous renal replacement therapy results in more hemodynamic instability than experienced with intermittent hemodialysis.
C. The use of continuous veno-venous hemodiafiltration (CVVHDF) is a combination of convective and diffusive clearance utilizing both replacement fluids and a dialysate solution.
D. When the combined volume of the hemofilter and circuit is more than 10% of the patient blood volume, the continuous veno-venous hemofiltration circuit may be primed with normal saline rather than blood.

5. A 3-year-old child with resolving methicillin-resistant *Staphylococcus aureus* sepsis and dialysis-dependent acute kidney injury has been found to have a toxic level of vancomycin. Which of the following is most accurate regarding its clearance with renal replacement therapy?
   A. Continuous renal replacement therapy in a convective mode may be useful to treat rebound high levels 4 hours after initial dialysis.
   B. Continuous veno-venous hemodialysis is more effective than continuous veno-venous hemofiltration in clearing vancomycin.
   C. Dialysis is not effective in the clearance of vancomycin.
   D. Peritoneal dialysis is the most effective renal replacement therapy to rapidly clear toxic vancomycin levels.

6. A 12-year-old female status post allogeneic hematopoietic cell transplant is admitted to the pediatric intensive care unit with severe *Streptococcus viridans* sepsis, grade IV acute graft-versus-host disease, hepatic failure, and acute kidney injury requiring continuous veno-venous hemodiafiltration with citrate anticoagulation. She is noted to have a steadily increasing total calcium level but a decreasing ionized calcium level. Which of the following interventions would be most likely to resolve this clinical concern in calcium levels?
   A. Decrease the rate of the citrate infusion.
   B. Decrease the replacement fluid infusion rate.
   C. Increase the rate of the calcium infusion.
   D. Decrease the rate of the dialysate.

7. Which of the following clinical situations is most likely to be associated with dialysis disequilibrium?
   A. A 3-hour course of hemodialysis that resulted in a decrease in the blood urea nitrogen concentration from 153 mg/dL (pre-dialysis) to 70 mg/dL (post-dialysis).
   B. A 12-hour course of peritoneal dialysis with short dwell times and a 4.25% dextrose dialysate solution resulting in a blood glucose concentration increase from 83 mg/dL to 192 mg/dL.
   C. A 2-hour course of hemodialysis that resulted in a decrease in the systolic blood pressure from 145 mm Hg to 98 mm Hg.
   D. The use of citrate anticoagulation for continuous veno-venous hemofiltration that produced a rise in the patient total calcium level to 12.2 mg/dL and a fall in the ionized calcium concentration to 0.97 mmol/l (normal range 1.22 to 1.37 mmol/L).

Answers

1. C
2. C
3. A
4. C
5. A
6. A
7. A

Suggested Reading

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Infectious Disease

Contents

Acute Pulmonary Infections

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Contents

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Learning Objectives

- Describe the epidemiology of acute pulmonary infections that require pediatric intensive care.
- Describe the signs and symptoms of bronchiolitis and pneumonia.
- Explain host defense mechanisms during acute pulmonary infections.
- State the common etiologies of bronchiolitis.
- State the common etiologies of pneumonia.
- Describe the pathophysiology of bronchiolitis and pneumonia in children.
- Describe the treatment options, including modes of ventilation, for bronchiolitis and pneumonia.
- Summarize an effective management strategy for parapneumonic effusions and empyemas.

33.1 Introduction

Acute lower respiratory infection is a common cause of morbidity in infants and children and, at times, requires intensive care and mechanical ventilation. Viral bronchiolitis and bacterial pneumonia account for the majority of lower respiratory tract infections that lead to respiratory insufficiency and pediatric intensive care unit admission. Twenty-seven percent of children who require mechanical ventilation for at least 24 h in pediatric intensive care units are diagnosed with bronchiolitis, and 16% have the diagnosis of pneumonia. The median length of time intubated for an acute pulmonary infection leading to respiratory failure is approximately 7 days.

Viral bronchiolitis remains the leading cause for hospital admission in infancy; peak incidence is between 3 months and 6 months of age, and it is the most frequent cause of acute respiratory failure in children admitted to pediatric intensive care units in North America. Pneumonia in children younger than 5 years of age has an annual incidence of 34–40 cases per 1000 population at risk. Community-acquired pneumonia can also lead to severe respiratory compromise especially in children with preexisting disease. A detailed understanding of the diverse etiologies and distinct clinical courses of acute pulmonary infections is essential for the pediatric critical care practitioner. This chapter will focus on bronchiolitis and pneumonia as the two leading causes of pulmonary infections leading to PICU admission.

33.2 Bronchiolitis

33.2.1 Epidemiology

Mortality from RSV bronchiolitis continues to decline with better intensive care and the use of preventive therapies.

Approximately one-third of children develop bronchiolitis during the first 2 years of life, with peak incidence between 3 and 6 months of age. Of these, 2–3% require hospitalization, accounting for 16% to 18% of yearly hospitalizations. Overall mortality rate for all children remains low at 1–2% but as high as 5% in high-risk infants. Most deaths occur in infants younger than 6 months of age with comorbidities such as prematurity, congenital heart disease, congenital or acquired lung disease, or immunodeficiency.

33.2.2 Etiology of Viral Bronchiolitis

Bronchiolitis was originally described by Wilhelm Lange in 1901. Respiratory syncytial virus (RSV) was first isolated in 1957 and still represents the major cause of bronchiolitis. Other causative viruses include enterovirus/rhinovirus, influenza, human metapneumovirus, parainfluenza, adenovirus, coronavirus, and human bocavirus. In the northern hemisphere, RSV outbreaks occur from October to April and account for 40–80% of cases. Human rhinovirus/enterovirus is isolated from 15% to up to 39% of cases. Rhinovirus has a bimodal peak; the first is between April and May and then again between September and October. Human metapneumovirus (hMPV) was discovered in 2001 and is linked to approximately 7% of bronchiolitis infections. Parainfluenza infections peak at 10 months of age, representing approximately 3% of cases of bronchiolitis. Parainfluenza 3 (PIV-3) is endemic throughout the year but especially common in the late spring. Human bocavirus (HBoV) was identified in 2005 as a cause of upper respiratory infections. It is rarely isolated as a sole pathogen and instead is identified as a coinfection in bronchiolitis 80% of the time. While adenovirus has been associated with bronchiolitis, it is more likely to cause a necrotizing pneumonia. Up to 30% of children are found to have coinfections with two viruses, most commonly RSV and rhinovirus.

Males are 1.5–2 times more likely to require hospitalization for bronchiolitis and are likely to have more severe disease. An X-linked genetic trait that results in a reduced tolerance to hypoxia has been postulated and would be consistent with the observation of increased mortality in newborn males with infant respiratory distress syndrome. Virtually all children by the age of 2 will have been infected with RSV, all children by the age of 5 will have been infected with hMPV, and all children by the age of 9 will have been infected with HBoV.

Male infants are more likely to require hospitalization and usually manifest more severe disease.

33.2.3 General Presentation and Pathophysiology

The classic presentation begins with nasal discharge progressing to lower respiratory tract symptoms of persistent cough, tachypnea, and increased work of breathing. The timing of symptoms is variable. Young infants may present with apnea prior to other respiratory symptoms. Auscultatory findings include inspiratory crackles and expiratory wheezing with the hallmark feature of minute-to-minute variability. Bronchiolitis is characterized by extensive inflammation and edema of the airways with increased mucus production and necrosis of airway epithelial cells. This cellular debris and mucus can plug the bronchiole lumen leading to obstruction and air trapping. About one-third of infants will have fever that is usually less than 39 °C. Although the majority of infants will have normal radiographs, infants with more severe disease will have peribronchial thickening, hyperinflation, and atelectasis, especially of the right upper lobe. The median duration of symptoms is 2 weeks. Risk factors for severe disease include chronic lung disease of prematurity, hemodynamically significant heart disease, immunodeficiency, neuromuscular disorders, and young infants with history of prematurity, especially <32 weeks gestation.

The remainder of the discussion on bronchiolitis is divided into RSV and non-RSV bronchiolitis. Although etiologic agents may differ, clinical courses are often similar.

33.2.4 Respiratory Syncytial Virus (RSV)

About one-half of all infants will be infected with RSV bronchiolitis in their first year of life; 3% will be hospitalized and 10% of hospitalized infants will require mechanical ventilation.

Respiratory syncytial virus (RSV) accounts for 50–80% of bronchiolitis, infecting one-half of all infants within the first year of life and hospitalizing approximately 120,000 infants yearly (about 3% of affected infants). Approximately 10% of these infants require mechanical ventilation with more than 200 deaths annually. Coinfection with either hMPV or rhinovirus occurs in 10–30% of young children.

Two types of RSV exist – types A and B. Type A is more common and is believed to cause more severe disease, although data is not conclusive. Both types may exist simultaneously in the community. Infants less than 1 year will typically shed the virus for about 9 days. Children with immunodeficiencies may shed the virus for months. The immune response varies with age and contributes to both termination of the disease and its pathologic features.

The virus is transmitted by respiratory droplets following close contact with infected persons or by contact with contaminated objects or surfaces. The mean incubation period is 4–6 days. There is a 45% RSV transmission rate within families and about one-half of hospital workers will acquire RSV. Therefore, hand washing and the wearing of gowns and gloves is of primary importance to attenuate transmission.

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33.2.5 Pathophysiology

33.2.5.1 Antibody-Mediated Immunity

RSV introduced onto the nasal or conjunctival mucosal surface causes profuse rhinorrhea within a few days. During the first 2 months of life, passively acquired maternal antibodies are protective. However, as maternal antibody titers gradually decrease, infants become susceptible to severe disease. Cell-bound IgA may develop to help clear the virus. Circulating IgG directed against the glycoprotein (G) and fusion (F) proteins (operative in syncytia formation) on the viral surface will develop several days later. Infants less than 3 months of age appear to induce a weaker antibody response likely due to the presence of maternal antibodies. Virus-specific IgE in the respiratory tract is associated with disease severity. Often, complete and effective immune responses are not induced; thus reinfections are possible even during the same season.

33.2.5.2 Cell-Mediated Immunity

Upregulation of the inflammatory cascade with release of chemokines and cytokines is contributory to the airway inflammation and hyperreactivity.

Epithelial cells and alveolar macrophages are key activators of cellular immunity. Although these cells enhance viral clearing, they also contribute to airway inflammation through the release of cytokines and chemokines. These include interleukin (IL)-1, tumor necrosis factor-alpha, IL-6, IL-8, macrophage-inflammatory protein (MIP)-1-alpha, and RANTES (regulated upon activation, normal T cell expressed and secreted). Release of these cytokines and chemokines is believed to be partially responsible for airway inflammation and hyperreactivity. The effects of these mediators persist beyond the acute infection and contribute to prolonged pulmonary dysfunction.

Children who require mechanical ventilation have lower peripheral T cell counts compared to hospitalized infants not requiring mechanical ventilation. Mechanically ventilated infants demonstrate low T cell proliferative responses and interferon (IFN-γ) production. IL-12 is required for the initiation of cellular immunity. The duration of mechanical ventilation was found to be inversely related to IL-12 production. The role of Th1-/Th2-like cytokine profiles, expressed as IFN-γ/IL-4 ratios, is controversial. In some studies, these

ratios decreased after polyclonal stimulation in hospitalized infants with RSV. However, more recent studies have shown normal ratios following polyclonal stimulation.

Neutrophils are the predominant cell found in the airways of infants with RSV bronchiolitis. IL-8 is found in high concentrations in the nasal secretions of infected children and acts as a neutrophil chemoattractant. Further evidence of cellular induced injury is seen in postmortem examination where peribronchial lymphocyte infiltration with bronchial epithelial necrosis is typically present.

33.2.6 Clinical Presentation and Course

Infants typically present with tachypnea, rhinorrhea, cough, low-grade fever, irritability, poor feeding, and vomiting. Respiratory rates greater than 60 breaths per minute are often associated with room air oxygen saturations of less than 96%. Infants may also have tachycardia, mild conjunctivitis, otitis media, or pharyngitis. Low-grade fever usually persists for 1–3 days. In addition, infants may develop a metabolic acidosis from poor caloric and fluid intake.

Apnea often is the first presenting symptom of RSV bronchiolitis in small infants. The etiology of apnea remains unknown; however, it is likely related to the immaturity of the respiratory control center in the brainstem. The incidence of apnea in infants with bronchiolitis is approximately 16–20%.

The heterogeneous nature of RSV-induced lung disease can cause atelectasis in some areas and overdistension in others. Chest roentgenograms often show hyperinflation with flattening of the diaphragms and patchy or peribronchial infiltrates. Atelectasis, especially of the right upper lobe, is often seen. Infants may have high lung volumes with the functional residual capacity often being twice normal. The decrease in dynamic compliance and increase in airway resistance leads to marked increase in work of breathing, often worse during expiration due to lower airway obstruction. Alterations in gas exchange and hypoxemia are secondary to a ventilation-perfusion mismatch.

The anatomical differences between young infants and older children contribute to the severity of the disease in the young. Due to the highly compliant cartilaginous chest wall and underdeveloped thoracic musculature, the infant's chest wall has difficulty countering the lung's inherent tendency toward collapse. Infants' smaller airways are more easily obstructed by secretions. These characteristics lead to a greater propensity toward atelectasis. The absence of effective collateral ventilation in infants also contributes to the development of atelectasis and impaired gas exchange. Cellular debris in small airways and peribronchial edema increase airway resistance leading to wheezing as the predominant symptom in some infants.

Despite the potential for severe impairment in lung function, most hospitalized infants improve within 3–5 days. Typically, by 2 weeks, they have normal respiratory rates, oxygenation, and ventilation. Chest radiographs usually normalize by day 9. However, about 20% of infants will have a protracted course, with some mild respiratory symptoms persisting for months.

Viral respiratory infections have been linked to the development of asthma later in childhood. The Tucson Children's Respiratory Study group prospectively followed for 13 years 880 infants who had bronchiolitis and found an increased risk for subsequent wheezing episodes. Additional studies including the Danish Copenhagen Prospective Study of Asthma in Childhood and COAST study support the hypothesis that early viral infections are a marker of

atopic predisposition. Both hypotheses may be correct with two different mechanisms at play. Seasonal RSV infections can produce a cytopathic effect in the airways, and rhinovirus outbreaks throughout the year often are associated with a family history of asthma or atopy.

33.2.7 High-Risk Populations

Some infants are at an increased risk for severe RSV disease such as those with chronic lung disease due to prematurity (bronchopulmonary dysplasia), cystic fibrosis, congenital heart disease, and immunodeficiencies. In children with cystic fibrosis, RSV accounted for 18% of symptomatic infections, 33% of hospitalizations for infants less than 1 year, and 43% of infants requiring mechanical ventilation. In a study of hospitalized infants with congenital heart disease (primarily cyanotic lesions or pulmonary hypertension) infected with RSV, 33% required intensive care, 19% received mechanical ventilation, and 3.4% died. Children having undergone hematopoietic stem cell transplants who develop RSV infections have an extremely high mortality of 60–80% despite mechanical ventilation and antiviral therapy. Environmental factors such as crowding, passive exposure to tobacco smoke, and lack of breast-feeding are associated with the development of severe disease. Compared to national averages, Native American and Alaskan children younger than 1 year of age have higher rates of infections.

33.2.8 Non-RSV Bronchiolitis

33.2.8.1 Rhinovirus/Enterovirus

Rhinovirus (RV) and enterovirus (EV) are leading causes of upper respiratory tract infections worldwide. After RSV, they are the most common viruses detected in hospitalized children. There are three distinct RV – A, B, and C – and four EV: A, B, C, and D. In 2014, EV-D68 was isolated as the cause for a large nationwide (49 states and the District of Columbia) outbreak in the US pediatric population. The RV and EV are closely related genetically and hence are not differentiated by nucleic acid amplification by PCR due to cross-reactivity of the assay. Children are the major reservoir and experience up to 8–12 infections per year. Infections occur all year but have two peaks: the first in April to May and the second from September to October. RV-C may peak more in the winter months and may contribute to more severe lower respiratory tract infections in children. RVs enter via the upper respiratory tract and bind to respiratory epithelial cells via several receptors, depending on the species. This attachment elicits an innate immune response leading to airway inflammation and remodeling. Until recently, RVs were thought to only infect the upper respiratory tract, but studies have demonstrated susceptibility of bronchial epithelial cells. Preexisting epithelial injury enhances RV replication, which may explain more severe disease in children with asthma or preexisting lung disease. RV tends to affect older children and has a milder and shorter clinical course in previously healthy children. However, as RV/EV often affects children with underlying cardiorespiratory or immunocompromised conditions, their clinical course may be more severe.

33.2.8.2 Parainfluenza

There are three subtypes of human parainfluenza viruses. PIV-3 (occurs late spring to early summer each year) is most frequently isolated from children with bronchiolitis, while PIV-1 (occurring in the fall of odd years) and PIV-2 (occurs in fall each year) most commonly cause croup. About 25% of children with PIV bronchiolitis admitted to the hospital require oxygen therapy, and 3% were admitted to the intensive care unit. Similar to RSV, both cell-mediated hyper-responsiveness to viral antigen and virus-specific IgE responses are observed in children with parainfluenza bronchiolitis. Upper airway edema with concomitant obstructive symptoms may be present.

33.2.8.3 Metapneumoviruses

The human metapneumoviruses (hMPV) are a group of RNA viruses of the *Paramyxoviridae* family identified in humans in 2001. There are two major genetic lineages, A and B. Although both genotypes can co-circulate, the dominant lineage may vary year to year. Group A is associated with more severe clinical symptoms. Infection has a seasonal distribution similar to RSV and influenza. The majority of children are born with maternal hMPV-specific IgG which wanes to around 25% by 6–12 months of age. By age 5, essentially 100% of children have been exposed to hMPV and will have neutralizing antibody to hMPV. Clinical presentation of children with this virus is similar to RSV. The pulmonary inflammation generally peaks on day 5 which includes interstitial edema and inflammatory cell infiltrates of the bronchioles and alveoli. These inflammatory changes can persist for up to 21 days. About half of infected children are 0–12 months of age. Immunity is incomplete and reinfections occur throughout adult life.

33.2.8.4 Human Bocavirus

Human bocavirus (HBoV) was discovered in 2003. With amino acid sequencing, this new member of the *Parvoviridae* family was found to be closely related to the bovine parvovirus and the canine minute virus, hence the name bocavirus (BO for bovine and CA for canine). The seasonality is unclear but appears to involve primarily the colder months. It remains undetermined if HBoV is a primary pathogen or acts to exacerbate other viral illnesses. Studies have reported HBoV in approximately 3% of children with respiratory tract infections. In a cohort of pediatric patients in Quebec, HBoV was detected in 14% of symptomatic children and 43% of asymptomatic children. A coinfection was detected in 71% of patients, consistent with other studies reporting 35–90% coinfection rates. Where earlier studies detected very low (1%) detection of HBoV DNA in asymptomatic patients, these tests were performed on nasal swabs. The Quebec cohort analyzed nasopharyngeal aspirates or bronchoalveolar lavage samples, supporting an increased incidence in the lower respiratory tract. In their population, none of the children with isolated HBoV infection required admission to the intensive care unit. Other studies have identified only HBoV as the causative agent in bronchiolitis and support that these patients generally have milder clinical symptoms. The pathogenesis of HBoV has not been well described, but with the high occurrence of wheezing and lower respiratory tract symptoms in children infected with the virus, it is speculated that this virus may be a significant contributor to asthma exacerbations. The majority of infected children have rhinorrhea, cough, and wheezing; however, diarrhea has been reported in up to 25% of these children. In children with high viral loads, HBoV has been detected in the serum suggesting the potential for disease beyond the respiratory tract.

33.2.8.5 Coronavirus

Human coronaviruses (CoV) were first described in the 1960s in patients with the common cold. In humans, CoV infections primarily involve the upper respiratory tract and the gastrointestinal tract with varying disease severity ranging from the common cold to bronchiolitis and pneumonia. In general, CoV infections occur in the winter season in temperate climates. The typical clinical course lasts several days and is indistinguishable from other viral respiratory pathogens. More recently, two strains of CoV were discovered that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which are discussed in the viral pneumonia section.

33.2.8.6 Influenza A and B

Both influenza A, including novel influenza strains such as H1N1, and influenza B can cause a clinical picture consistent with bronchiolitis in the small infant. These viruses may cause severe multisystem disease and are discussed in greater detail in the viral pneumonia section.

33.2.8.7 Diagnosis

Molecular assays are the recommended test for respiratory virus detection. The published sensitivities and specificities approach 100% when compared to tissue culture or antigen assay. These assays generally use nucleic acid amplification by polymerase chain reaction. The assay results are available in 30–60 min. The most important cause of false-negative test results remains poor specimen handling or inadequate sample collection. Other than aiding with cohorting of hospitalized patients, detection and identification of respiratory viruses is rarely clinically useful.

33.2.8.8 Treatment

Regardless of the viral etiology of bronchiolitis, supportive care remains the mainstay of treatment (◘ Table 33.1). Supplemental humidified oxygen is frequently needed. Titrating oxygen to maintain oxygen saturations at 90% is shown to be safe and provide adequate tissue oxygenation. It is common for infants and children to have intermittent, brief episodes of hypoxemia that, if left untreated, does not cause impairment in intellect or behavior. As many infants are obligate nasal breathers, nasal suctioning may be beneficial to maintain an unobstructed upper airway. A retrospective study reported that deep suctioning was associated with longer lengths of stay; thus, routine deep suctioning may not be beneficial. A Cochrane review found no benefit in chest physiotherapy by vibration, percussion, or passive expiratory techniques.

The affected infant or child is often unable to take adequate fluids complicated by increased insensible losses from the respiratory tract. About one-third of infants hospitalized with bronchiolitis require intravenous fluids. Stable infants, especially those with respiratory rates exceeding 60–70 breaths per minute, are often not able to take adequate feeds, but generally tolerate nasogastric feeds. Infants and children with severe respiratory distress should be kept NPO in the event respiratory failure ensues and endotracheal intubation is required. Some infants and children may develop fluid retention secondary to increased production of antidiuretic hormone.

Supportive therapy is the mainstay of treatment for bronchiolitis. Ribavirin, bronchodilators, and corticosteroids have not shown benefit.

Antibiotics are not routinely indicated in previously healthy children. In a 9-year prospective study of 565 children with RSV by Dr. Hall, a concurrent bacterial infection was found in only 1.2%. However, the incidence of bacterial coinfection may be increased in infants and children who develop respiratory failure requiring mechanical ventilation. The Royal Liverpool Children's Hospital group collected lower airway secretions by bronchoalveolar lavage

Table 33.1 2014 AAP clinical practice guidelines

1	Clinicians should not administer albuterol to infants and children with bronchiolitis
2	Clinicians should not administer epinephrine to infants and children with bronchiolitis
3a	Nebulized hypertonic saline should not be administered to infants with bronchiolitis in the ED
3b	Clinicians may administer nebulized hypertonic saline to hospitalized infants and children with bronchiolitis
4	Clinicians should not administer systemic corticosteroids to infants and children with bronchiolitis
5a	Clinicians may choose to not administer supplemental oxygen if oxyhemoglobin saturations exceed 90% in infants and children with bronchiolitis
5b	Clinicians may choose not to use continuous pulse oximetry for infants and children with bronchiolitis
6	Clinicians should not use chest physiotherapy for infants and children with bronchiolitis
7	Clinicians should not administer antibacterial medications to infants and children with bronchiolitis unless there is a concomitant bacterial infection or strong suspicion of one
8	Clinicians should administer nasogastric or intravenous fluids for infants and children with bronchiolitis who cannot maintain hydration orally

(BAL) within 3 h of endotracheal intubation in 165 infants and children with documented RSV infections. Twenty-one percent were found to have a coinfection with $>10^5$ cfu/mL bacteria. Of the 98 children in this study with any bacteria isolated by BAL, 23% had multiple organisms. Interestingly, 45% of these patients had received antibiotics prior to endotracheal intubation. Dr. Hall and colleagues also found a significantly greater proportion of bacterial infections occurring in children who had received parenteral antibiotics. An abnormal white blood cell count is not useful for predicting a concurrent bacterial infection. Approximately 25% of hospitalized infants with bronchiolitis will have radiologic evidence of atelectasis, making it difficult to distinguish a bacterial infiltrate or consolidation. Procalcitonin concentrations >1 ng/L have shown some promise in differentiating viral and bacterial pneumonia.

High-risk patients often require close monitoring and care in an intensive care unit. These include infants less than 6 weeks of age or infants with a history of prematurity, congenital heart disease, bronchopulmonary dysplasia, immunodeficiency, or neurologic disease. Infants with RSV bronchiolitis typically have a combination of hyperinflation, pulmonary infiltrates, and atelectasis. Therefore, no one mode of ventilation can be recommended for all infants. Humidified, heated high-flow nasal cannula (HFNC) to deliver air-oxygen mixtures can improve respiratory effort and generate positive airway pressure. Evidence suggests it reduces work of breathing and may decrease the need for intubation. Other noninvasive positive pressure (NIPP) modes (CPAP or BiPAP) may be attempted in infants and children where their primary respiratory embarrassment is secondary to atelectasis. However, this may not be suitable if the disease process appears severe or protracted as prolonged use of NIPP may make feeding difficult, cause breakdown of facial tissue, or be dif-

ficult to maintain without significant sedation that further compromises ventilation. If an infant requires endotracheal intubation, the mode of mechanical ventilation should be tailored to the predominant lung pathology present (i.e., atelectasis versus hyperinflation). Children with significant air trapping may need mechanical ventilation similar to a child with asthma, providing relatively low respiratory rates and longer inspiration and exhalation times. The more typical infant loses functional residual capacity (FRC) because of atelectasis and alveolar infiltrates. Therefore, despite having some air trapping, these infants often need PEEP adjusted to recruit alveoli and return FRC to normal. In the setting of elevated pulmonary vascular resistance (PVR) that may occur in infants with congenital heart disease or bronchopulmonary dysplasia, lowering PVR by traditional methods such as maintaining oxygenation, deep sedation, muscle relaxation, and even nitric oxide may be indicated.

Ribavirin is the only FDA-approved antiviral drug for RSV. Ribavirin inhibits viral replication and is active against RSV, influenza A and B, adenoviruses, and hepatitis viruses. For lower respiratory tract diseases, ribavirin is typically administered via aerosolization. In 1996, a meta-analysis of studies involving ribavirin was discouraging and was consistent with the common clinical experience that ribavirin did not improve clinical outcomes. Therapy targeted at attenuating the virus-induced inflammatory cascade has also been disappointing. Corticosteroid administration was not associated with reduction in clinical scores, the need for hospitalization, or the length of hospitalization. Routine use of any corticosteroid given via any route (intravenous, enteral, or aerosolized) is not indicated, except in patients with preexisting chronic lung disease.

Bronchodilators have not shown a clear benefit in patients with acute RSV bronchiolitis. In 12 randomized controlled trials involving 843 infants, evaluating the effect of salbutamol or albuterol on bronchiolitis, 9 (75%) showed no effect. The remaining three studies demonstrated only a small transient improvement in the acute clinical score. The original AAP clinical guidelines included a trial of β-adrenergic agonists as an option. However, given additional evidence demonstrating no benefit, this recommendation has been removed. It is recognized that a small subset of children may have reversible airway smooth muscle constriction responsive to β-adrenergic agonists. Also, children with severe disease or with respiratory failure were excluded from all these trials, so evidence cannot be generalized to this population.

A recent Cochrane meta-analysis found no evidence to support the use of nebulized epinephrine for inpatients. Two large multicenter randomized trials of nebulized epinephrine found no improvement in length of stay or outcomes when compared to placebo or albuterol. Evidence remains controversial regarding its use in the outpatient setting where a systematic review concluded that it might reduce hospitalizations.

Nebulized hypertonic saline increases mucociliary clearance in both normal and diseased lungs. With inflammation and mucus plugging prominent in bronchiolitis, hypertonic saline should be beneficial. Studies have shown it to be safe and effective in improving symptoms in mild-to-moderate bronchiolitis. However, a 2013 Cochrane review along with additional randomized controlled studies did not demonstrate a significant decrease in the length of hospitalization or in reducing hospital admissions. Like many other treatments, its use has not been studied in the intensive care setting.

Several studies evaluated the benefit of surfactant and nitric oxide for severe respiratory distress. There are a few preliminary studies that report inhaled nitric oxide to be safe and possibly decrease length of hospitalization. A Cochrane review of surfactant for the treatment of bronchiolitis also showed a

favorable effect on duration of mechanical ventilation, duration of ICU stay, as well as improved oxygenation and ventilation. However, the number of studies was small with only 79 subjects in total. Heliox, a mixture of oxygen (20–30%) and helium (70–80%) resulting in lower viscosity than air, has been used successfully in cases of airway obstruction, croup, airway surgery, and asthma to reduce respiratory effort during the period of airway compromise. A Cochrane review of 447 infants with viral bronchiolitis suggested a reduced clinical score for respiratory distress in the first hour after starting heliox treatment, but did not show a decrease in intubation rate or in the length of treatment.

33.2.8.9 Prevention

Palivizumab should be used as preventive therapy in infants with chronic lung disease and congenital heart disease. Cardiopulmonary bypass significantly lowers the serum level of palivizumab, so it should be redosed following surgery if continued protection is desired.

Palivizumab (Synagis™) is a neutralizing humanized mouse monoclonal antibody directed against the RSV-F glycoprotein. It was licensed by the Food and Drug Administration (FDA) in 1998 for premature infants and infants with bronchopulmonary dysplasia. The randomized, double-blind, placebo-controlled IMpact-RSV trial involving 1502 high-risk infants found a significant (55%) reduction in hospitalizations. With the exception of very rare anaphylaxis, no significant adverse effects have been observed. Palivizumab has been approved for use in infants with congenital heart disease. The cardiac Synagis study group included 1287 children with congenital heart disease in a randomized, double-blind, placebo-controlled trial; it found a 45% relative reduction in RSV-associated hospitalizations with no deaths attributable to the palivizumab. Since cardiopulmonary bypass can decrease serum drug concentrations by about 58%, it is recommended that an additional dose be given following cardiac surgery, if continued protection is desired.

In 2014, the American Academy of Pediatrics updated the guidelines for the administration of palivizumab (Table 33.2). It should be administered intramuscularly as 15 mg/kg every 30 days for a total of five doses during RSV season, which is generally from November through March, to high-risk infants. This includes preterm infants born before 29 weeks, infants with hemodynamically significant congenital heart disease, and infants with chronic lung disease

Table 33.2 2014 AAP clinical practice guidelines for prevention

1	Clinicians should administer palivizumab during the first year of life to infants with gestational age <29 weeks, 0 days
2	Clinicians should administer palivizumab during the first year of life to infants with hemodynamically significant heart disease
3	Clinicians may administer palivizumab during the first year of life to infants with chronic lung disease of prematurity defined as preterm infants <32 weeks, 0 days gestation who require >21% oxygen for at least the first 28 days of life
4	Clinicians should administer a maximum of five monthly doses (15 mg/kg/dose) of palivizumab during the respiratory syncytial virus season
5	All people should disinfect hands before and after direct contact with patients, inanimate objects in the direct vicinity of the patient, and after removing gloves
6	All people should use alcohol-based rub for hand decontamination; if not available, wash with soap and water
7	Clinicians should counsel about the harm from exposing infants or children to cigarette smoke
8	Clinicians should encourage breast-feeding for at least 6 months to decrease morbidity of respiratory infections

of prematurity that required oxygen for >28 days. These infants should also receive palivizumab in their second year of life if they continue to require oxygen, diuretics, or corticosteroids. Infants or children who develop an RSV infection should continue to receive prophylaxis following recovery because the naturally acquired antibodies are not fully protective.

33.3 Pneumonia

Pneumonia describes any inflammatory condition of the lung involving the alveoli. In response to inflammation, the alveoli become filled with inflammatory fluid, inflammatory cells, and cellular debris. Infection is the primary cause of parenchymal injury to the lung. Causative pathogens include viruses, bacteria, and fungi. Alveolar inflammation may also result from aspirated foreign matter.

33.3.1 Clinical Presentation

Signs and symptoms of pneumonia are nonspecific and may be occult in the young infant. Children often have fever, chills, headache, malaise, restlessness, and irritability. Gastrointestinal complaints such as abdominal pain, distention, or emesis may also be present in young children. The symptoms are often preceded by minor upper respiratory tract infections characterized by low-grade fever and rhinorrhea. With more significant involvement of the lower respiratory tract, tachypnea, dyspnea, cough, nasal flaring, grunting, or retractions may be seen. The older child may demonstrate productive sputum and complain of pleuritic chest pain. On auscultation of the chest, crackles and/or decreased breath sounds might be heard over areas of consolidation or pleural effusions. However, due to the short path for transmission of breath sounds and the small chest size in infants, breath sounds may not be decreased, even in the presence of effusions. Children with pleural irritation might prefer to lie on the affected side with legs flexed and may complain of radiating pain to the neck and shoulder or into the abdomen. A systematic review suggests that hypoxemia, altered mental status, age < 6 months, dyspnea, multilobar infiltrates, and moderate/large pleural effusions are the factors most predictive of pneumonia severity in children.

33.3.2 Epidemiology

Community-acquired pneumonia (CAP) is defined as an acute infection of the lung parenchyma that was acquired outside the hospital. It is a common, and at times, a serious infection in children. The incidence has decreased substantially in recent decades due to improved socioeconomic conditions, better access to care, implementation of effective management and preventive strategies, and development of vaccines. The Global Burden of Diseases study estimated that pneumonia accounted for almost 900,000 of the 6.3 million deaths in children in 2013. The incidence of pneumonia in children under 5 years of age in affluent countries is estimated at 0.015 episodes per child year compared to 0.22 episodes per child year in low- and middle-income countries. The exact prevalence of the etiologic agents causing pediatric pneumonia is difficult to ascertain. It is often difficult to differentiate viral from bacterial pneumonia

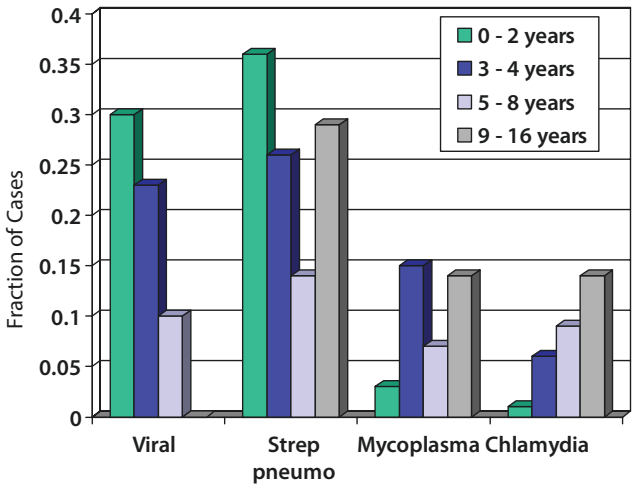

Fig. 33.1 Etiology of community-acquired pneumonia based on age

based solely on clinical examination. Specific pathogens causing CAP can be determined in only approximately one-third of children using commonly available cultures, antigen detection, or serologic techniques. Blood cultures yield pathogens in only about 10% of infants and children with bacterial CAP. With these inherent limitations, it is generally thought that viruses account for approximately 80% of CAP in children under the age of 2 years and approximately 50% of CAP in preschool children ages 2–5 years. Viral causes decline in the school age and adolescent child, and bacterial causes such as *Streptococcus pneumoniae* and *Mycoplasma* become important pathogens (Fig. 33.1).

It is difficult to determine the etiologic agent causing pneumonia, but when microbial agents are identified, bacteria are isolated in 20–30%.

Overall, bacteria may account for 15–20% of community-acquired pneumonias; however, it is often not possible to distinguish colonization from pathogenic bacteria. More recent meta-analyses suggest that clinical pneumonia may be caused by sequential or concurrent organisms. Severe disease is often caused by multiple pathogens. The likelihood of infection with different bacteria varies by age. In the newborn period, organisms from the maternal genital tract are likely causes and include *Group B Streptococcus*, *Escherichia coli*, enteric Gram-negative bacilli, *Listeria*, and *Chlamydia*. In older infants, *Streptococcus pneumoniae* becomes a significant cause. *Group A Streptococcus* and *Staphylococcus aureus* are uncommon causes. *Moraxella catarrhalis* is a common cause of upper respiratory tract disease but rarely causes pneumonia. About 20% of infants with pertussis will have bacterial coinfection. In children older than 6 years of age, *Streptococcus pneumoniae* remains the most common cause. *Haemophilus influenzae type B* (HIB), and most recently *Streptococcus pneumoniae*, have decreased significantly as causes of CAP due to the widespread use of effective vaccines.

In the older child and young adolescent, the atypical pneumonias, *Mycoplasma* and *Chlamydia*, become more prevalent and viral causes less common. Rare bacterial pneumonias can occur with animal contact and include *Francisella tularensis* (rabbits), *Chlamydia psittaci* (parrots and birds), *Coxiella burnetii* (sheep), and *Salmonella choleraesuis* (pigs). Children with congenital anatomical defects, immunodeficiencies, neurologic disorders, and genetic disorders are at increased risk for bacterial, viral, and fungal pneumonia.

33.3.3 Normal Host Defense Mechanisms

The airways are normally sterile below the sublaryngeal area to the lung parenchyma. There are several protective mechanisms that include anatomic and mechanical factors, local immune defenses, and the systemic immune response. Microbes are filtered by nasal hairs or are expelled from the airways by the epiglottic reflex, cough reflex, and mucociliary apparatus. Immunoglobulin A (IgA) is the predominant immunoglobulin present in the upper respiratory tract. IgA is able to bind two antigens simultaneously, forming large antigen-antibody complexes. In this manner, the microbes are neutralized and removed by ciliary clearance, thus preventing microbial binding to the epithelium. In the lower tract, immunoglobulin G (IgG) provides humoral protection by opsonizing microbes for phagocytosis by neutrophils and macrophages, activating the complement cascade, and by neutralizing bacterial endotoxin. Activated alveolar macrophages and/or neutrophils produce superoxide anions, hydrogen peroxide, and hydroxyl radicals that serve an important role in the host defense; however, uncontrolled production can lead to lung injury. In addition to oxygen radicals, a number of cytokines are produced by the alveolar macrophages. These include IL-1, IL-6, IL-17, TNF, transforming growth factor-β (TGF-β), chemotactic factors, platelet-derived growth factor, and macrophage colony-stimulating factor (M-CSF). These cytokines play a central role in phagocytic recruitment and activation.

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Pneumonia occurs when one or more of the host defense mechanisms are altered. Viruses enhance the host susceptibility to bacterial pathogens by affecting clearing mechanisms and by weakening the host immune response.

Infection occurs when one or more of the defense mechanisms are impaired, invasion by a virulent organism, and/or if the infectious inoculum overwhelms the defense mechanisms. Pathogens typically gain entry through inhalation of aerosolized material or through aspiration of resistant organisms inhabiting the upper airways. Less frequently, pneumonia can occur via hematogenous spread.

In children with bacterial pneumonia, a significant portion will have a concurrent or preceding viral infection. Viral infection may predispose to bacterial superinfection by reducing clearance mechanisms, weakening the host immune response, and allowing direct access via necrosis of the bronchial epithelium.

33.3.4 Pathophysiology

Pathogens entering the lower airways evoke an exudative consolidation of pulmonary tissues. Initially, there is hyperemia of lung parenchyma due to vascular engorgement and capillary leak causing exudation and intra-alveolar fluid accumulation. Fibrin is then deposited and the airways are infiltrated with neutrophils. Consolidation decreases lung compliance, vital capacity, and the alveolar surface area available for gas exchange. A physiologic shunt (V/Q mismatch) occurs as there is increased blood flow through poorly ventilated segments of the lung, resulting in hypoxemia. Compensatory hypoxic vasoconstriction may occur in an attempt to reduce V/Q mismatch and hypoxemia, especially in localized areas of consolidation.

With treatment, resolution of consolidation occurs in 8–10 days. The exudate undergoes enzymatic digestion and is either reabsorbed or removed by coughing. If the bacterial infection extends into the pleural cavity, an empyema may result.

33.4 Specific Etiologies

33.4.1 Bacterial Pneumonia

33.4.1.1 Streptococcus pneumoniae

Streptococcus pneumoniae is the most common bacterial cause for pneumonia.

Streptococcus pneumoniae is a Gram-positive diplococcus that is frequently found in the upper respiratory tract. There are over 80 capsular serotypes with 80% of infections caused by 14 serotypes. It is the most common bacterial cause for pneumonia occurring at a peak age of 13–18 months. Typically, it causes a lobar or segmental consolidation, but it may manifest as patchy infiltrates in infants. Pleural effusions occur in up to 20–60% of children who require hospitalization (◘ Fig. 33.2). Pneumatocele formation is rare. Hemolytic uremic syndrome is associated with neuraminidase-producing strains.

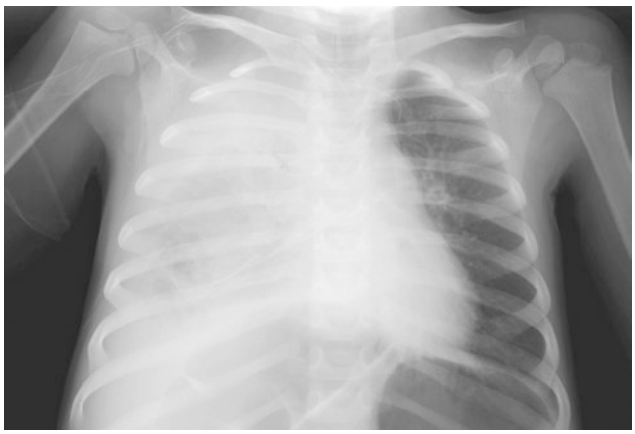
Treatment is typically with a penicillin or cephalosporin. Emerging antibiotic resistance may require initial therapy with vancomycin. In hospitalized patients, parenteral therapy is generally needed for 48–72 h after fever resolves, followed by completion of 7–10 days of enteral therapy.

Pneumococcal conjugate vaccines (PCVs) have been developed that confer immunity against 13 and 23 serotypes. The 13-valent PCV (Prevnar 13) was licensed for use in the United States in 2010. The PCVs have been highly effective at reducing hospitalizations for pneumococcal pneumonia.

PCV is now recommended universally for children younger than 24 months of age. The 23-valent PCV (Pneumovax) is available for high-risk children. This includes children with sickle cell disease and other types of functional asplenia, human immunodeficiency syndrome, and primary immunodeficiency, children receiving immunosuppressive therapy, and children with chronic pulmonary or cardiac disease. Children with sickle cell disease or functional asplenia should continue to receive antibiotic prophylaxis regardless of whether or not they received pneumococcal vaccines.

33.4.1.2 Chlamydia trachomatis

Approximately 50–75% of infants born to *Chlamydia trachomatis*-infected mothers will become infected at one or more anatomical sites, including the conjunctiva, nasopharynx, rectum, and vagina. About 30% of infants with nasopharyngeal infections will develop pneumonia. The infants usually present at about 2–12 weeks of age with staccato cough and congestion but an absence



◘ **Fig. 33.2** Chest radiograph of 3-year-old female with *Streptococcus pneumoniae* pneumonia. Note the combination of consolidation and effusion affecting the right lung. (Image provided courtesy of FA Maffei)

of fever. The cough often interferes with the ability to feed. Infants generally have tachypnea and crackles on examination and the chest x-ray frequently shows hyperinflation. A peripheral eosinophilia may be present. Diagnosis can be made through culture or nucleic acid amplification tests. *C. trachomatis* is susceptible to macrolides, tetracyclines, quinolones, and sulfonamides. Erythromycin for 14 days is the treatment of choice for neonatal pneumonia.

33.4.1.3 Chlamydia pneumoniae and Mycoplasma pneumoniae

Mycoplasma pneumoniae and *Chlamydia pneumoniae* have an increased prevalence in older children.

Mycoplasma pneumoniae and *Chlamydia pneumoniae* play a greater role in causing respiratory tract disease in children than previously thought. An indolent course that develops over 5–7 days manifested by low-grade fever, sore throat, aches, and headaches characterizes both pathogens. After a few days, crackles may be heard, particularly in the bases where the infiltrates tend to occur. These organisms have been associated with the initiation, promotion, and exacerbation of asthma in children. In addition, a pertussis-like illness with acute bronchitis has been described. The CDC Epic Study showed that *Mycoplasma pneumoniae* was identified in 8% of children admitted to the hospital for community-acquired pneumonia. They also demonstrated that the detection of *Mycoplasma pneumoniae* increased gradually throughout the fall and peaked in the winter. Classic atypical pneumonias caused by these organisms are usually mild and self-limited. However, a number of studies have suggested that severe pulmonary infection may occur in otherwise healthy children. Pleural effusions occurred in 26% of children in the CDC Epic Study. Pneumatoceles, lung abscesses, pneumothoraces, bronchiectasis, chronic interstitial fibrosis, and acute respiratory distress syndrome, although rare complications, have all been reported. Serological testing is the most common means of diagnosis, but this is often retrospective. There are many tests available including culture, cold agglutinin antibodies, serology, and PCR assays. Treatment with antibiotics reduces the rate of recurrent wheezing episodes, decreases morbidity, and shortens the duration of symptoms. The organisms are susceptible to tetracyclines, macrolides, and quinolones. The 2011 Infectious Disease Society of America (IDSA) Guideline for Management of Community Acquired Pneumonia in Infants and Children recommends treatment with a macrolide whenever there is suspicion for *Mycoplasma pneumoniae* infection. There is evidence of emerging resistance to macrolides with a rate of 4% in the United States. Persistent fever 48 h after initiation of therapy may indicate macrolide resistance, and a tetracycline or fluoroquinolone is the drug of choice in these situations.

33.4.1.4 Staphylococcus aureus

While *Staphylococcus aureus* pneumonia is uncommon, effusions ultimately develop in about 75% of cases, and pneumatoceles occur in 45–60%.

Staphylococcus aureus is a Gram-positive organism that can be found on the skin, nasal mucosa, and other mucus membranes. About 20–30% of children are carriers. It is generally spread by direct contact or by respiratory particles. *S. aureus* is an unusual cause of lower airway disease in otherwise healthy children (only 1% of children admitted to the hospital with community-acquired pneumonia were found to have *S. aureus* in the CDC Epic Study). It is more typically isolated from infants and young children with debilitating conditions. Primary *S. aureus* pneumonia presents in the winter or early spring with a short febrile prodrome and a rapid onset of pulmonary symptoms. Blood cultures are positive in 20–30% of patients. Secondary staphylococcal pneumonia will have a more prolonged prodrome with no seasonal predilection, but is often seen after influenza infections; in this setting, blood cultures are positive in about 90% of patients. Unilateral lobar disease is more typical with primary disease, while diffuse bilateral infiltrates are more frequent with secondary

pneumonia. Effusions can be diagnosed in about 15% of children at presentation but ultimately will develop in about 75% of cases. Pneumatoceles occur in up to 45–65% of children. Treatment is with cefazolin or oxacillin, but more organisms are becoming resistant and require therapy for serious or invasive disease with vancomycin, clindamycin, or linezolid.

Methicillin-resistant *Staphylococcus aureus* (MRSA) was once considered to be restricted to hospitals and long-term care facilities. However, community-acquired MRSA (CA-MRSA) is now a significant cause of a variety of infections (including pneumonia) in children without prior healthcare facility exposure. The majority of community-acquired MRSA infections involve minor skin and soft tissue infections, but invasive and sometimes fatal infections can occur in otherwise healthy individuals. CA-MRSA and healthcare-associated MRSA (HA-MRSA) can be distinguished by several important features. Patients with CA-MRSA by definition have not had recent hospitalization (acute or chronic care), prolonged antibiotic use, or chronic underlying disease. Toxin production also distinguishes CA-MRSA from HA-MRSA. Panton valentine leukocidin (PVL) is a toxin that is present in most CA-MRSA isolates but rarely in HA-MRSA isolates. PVL toxin lyses white blood cells leading to leukopenia and a decreased ability to kill *S. aureus*. Its production has been implicated as a contributor to the development of CA-MRSA necrotizing pneumonia. CA-MRSA isolates, unlike HA-MRSA, lack multidrug resistance. Thus, CA-MRSA is generally more susceptible to clindamycin, trimethoprim-sulfamethoxazole, and doxycycline than HA-MRSA, probably because HA-MRSA has developed resistance to survive in the healthcare setting.

33.4.1.5 Group A Beta-hemolytic *Streptococcus*

Group A beta-hemolytic Streptococcus (GABHS) is a Gram-positive organism responsible for about 15% of pharyngitis and tonsillitis in children. It is rare as a primary cause of pneumonia (1% in the CDC Epic Study). When it does occur, the children generally have high fever and appear toxic. The pneumonia is typically lobar. Associated empyemas are common and pneumatoceles may develop. There are several virulent toxin-producing GABHS M-serotypes that are associated with toxic shock syndrome. An associated pneumonia occurs in 10–20% of children with toxic shock syndrome. GABHS are highly susceptible to penicillins and cephalosporins. In cases of toxic shock, clindamycin is often added to inhibit the production of streptococcal pyrogenic exotoxins A (SPE-A) and B (SPE-B).

33.4.1.6 Group B *Streptococcus*

Early-onset disease (symptoms usually occur within 24 h of birth but can present within 6 days of birth) usually presents as sepsis, meningitis, or pneumonia. About 10% of infants with early-onset GBS will have pneumonia. Radiographic findings can be difficult to distinguish from hyaline membrane disease. The infant usually has systemic disease and blood cultures are frequently positive. Late-onset GBS usually occurs at 4–5 weeks of age and is predominantly caused by the type III serotype. In these infants, the infection is usually manifest as bacteremia without a focus or with meningitis; pneumonia is rare in late-onset disease. GBS is uniformly sensitive to penicillin.

33.4.1.7 Bordetella pertussis

Pertussis or "whooping cough" is a highly contagious respiratory tract infection caused by the Gram-negative pleomorphic bacillus *Bordetella pertussis* and less commonly *Bordetella parapertussis*. With the development and wide-

spread use of a vaccine in the 1940s, a significant and sustained decrease in incidence has occurred. There has been a slight increase in pertussis cases reported to the CDC in recent years with almost 18,000 reported in 2016. Under-immunized or unimmunized infants are the most vulnerable. Nearly all deaths reported from pertussis occur in infants younger than 3 months of age.

Pertussis is often divided into catarrhal (fever, rhinorrhea, and initiation of cough), paroxysmal (severe coughing episodes, lymphocytosis, potential for complications), and convalescent stages (slow waning of cough over weeks to months). Complications include secondary bacterial or viral pneumonia, apnea, malnutrition, pulmonary hypertension, and neurologic involvement including seizures and encephalopathy. Infants less than 6 months of age are at highest risk for morbidity and mortality. Characteristic paroxysms of cough with an end-inspiratory whoop occur in children. Infants may present with a nonspecific cough with associated apnea and cyanosis, without a whoop. Adolescents may be asymptomatic or have only a mild prolonged cough. An increased white blood cell count up to 100,000/μL with a lymphocytosis is characteristic early in the course of the disease. The preferred test for laboratory confirmation is the detection of *B. pertussis* DNA by PCR assay. Bacteriologic culture provides a definitive diagnosis.

If administered during the early stages of the disease (first 7–10 days of illness), erythromycin for 14 days may decrease symptoms and reduce the risk of spread. A 5-day course of azithromycin or a 7–10-day course of clarithromycin has been found to be as effective with less gastrointestinal symptoms than observed with erythromycin. Corticosteroids, bronchodilators, or intravenous immunoglobulins have not demonstrated efficacy. Supportive care with supplemental oxygen, mechanical ventilation, intravenous fluids, maintenance of adequate caloric intake, and treatment of secondary bacterial infections are the mainstay of therapy. The use of extracorporeal membrane oxygenation in infants with hypoxemia, pulmonary hypertension, and right heart failure refractory to conventional mechanical ventilation has resulted in poorer outcomes than expected. Vaccination is preventative.

33.4.2 Viral Pneumonia

Approximately 70–80% of pneumonias in children are caused by viruses. There is considerable evidence that viral infections often precede bacterial pneumonias causing weakening of the host defenses. Viral pneumonias with RSV and parainfluenza are discussed in more detail in the bronchiolitis section.

33.4.2.1 Influenza

Although death from influenza pneumonia is uncommon, a significant number of the children who died were previously healthy.

Influenza is the main viral cause of pneumonia in school-aged children requiring hospitalization. Annually, 870,000 children less than 5 years of age are hospitalized due to influenza. There are three serotypes, A, B, and C, which are further divided into subtypes based on the hemagglutinin and neuraminidase genes. Hemagglutinin 1, 2, and 3 and neuraminidase 1 and 2 typically infect humans. The gene segments for the surface glycoproteins are unstable. Only a few amino acid changes at critical sites regularly cause antigenic drift and a variant that is not recognized by antibodies acquired from previous infections or vaccines. In addition, genetic reassortment can occur via the exchange of entire gene segments when two different influenza viruses infect and replicate in the same host. This is frequently seen in aquatic birds, which are the main reservoir for influenza A, and in pigs that are susceptible to both avian and human influenza A viruses. Epidemics occur annually during the winter months with a short (1–3 days) incubation period. Devastating pandemics

have occurred in 1918, 1957, 1968, and 2009. The virus causes destruction of the ciliated respiratory epithelium within 1 day of symptoms. Airway edema and infiltration with inflammatory cells into the airway mucosa and epithelium follows. Slow repair occurs over 2–4 weeks. A severe fulminating pneumonia may result in hemorrhagic exudates that contain many polymorphonuclear and mononuclear cells. Destruction of the respiratory epithelium often leads to secondary bacterial infections.

In the 2017–2018 influenza season, 179 influenza-related pediatric deaths occurred; 43% were in otherwise healthy children, 26.2% had asthma or reactive airway disease, 16.8% had neurological disorders, and 10.5% were obese. Historically, 80–85% of pediatric deaths are in unvaccinated children 6 months and older. Rare complications of influenza include acute myositis, rhabdomyolysis, myocarditis, pericarditis, Reye syndrome, encephalitis, transverse myelitis, and Guillain-Barré syndrome.

Children may present with an abrupt onset manifested by high fever, myalgias, headaches, scratchy sore throats, and dry cough that generally lasts 4–7 days. Peripheral white blood counts are usually less than 5000/μL. Pulmonary infiltrates often involve multiple lobes. Bacterial coinfection, especially with MRSA, increases morbidity and mortality significantly.

Antiviral treatment with neuraminidase inhibitors, especially when given early, can reduce the severity and duration of symptoms. Children treated with oral oseltamivir within 48 h of symptom onset had a 36-h decrease in duration of illness, with greatest benefit in those receiving treatment within 24 h. However, no significant reduction in duration of illness was observed in children with asthma, despite improvement in pulmonary function as measured by forced expiratory volume at 1 s. Retrospective studies have observed a shorter hospital stay for children treated with oseltamivir. Zanamivir is a dry powder aerosol that must be delivered by a special breath-activated device; it should not be delivered via nebulizers, ventilators, or other aerosolized delivery devices. Children treated with zanamivir had a 1.3-day reduced median duration of illness. Zanamivir may increase the risk for bronchospasm and should generally be avoided in children with asthma or chronic lung disease. Intravenous peramivir was FDA approved in 2017 for uncomplicated influenza in children at least 2 years old who cannot tolerate oral oseltamivir or inhaled zanamivir. Studies of hospitalized pediatric patients are ongoing. Intravenous zanamivir will likely be made available if a newly emergent oseltamivir- or peramivir-resistant virus were to become a serious concern. Treatment with oseltamivir is recommended and has shown some benefit for children with serious, complicated, or progressive disease with proven or presumed influenza regardless of immunization status or onset of symptoms greater than 48 h. Amantadine and rimantadine are no longer recommended for treatment or prophylaxis due to the high rate of resistance of influenza A viruses.

In an observational study of 840 critically ill children, treatment with high-dose corticosteroids was associated with a higher risk of death. There is insufficient data to support treatment with immunoglobulin, although this is an area of active research. Aspirin or aspirin-containing products should be avoided due to the risk of Reye syndrome.

Immunoprophylaxis is the most effective strategy for the prevention of influenza infection. Inactivated vaccines have efficacy rates from 30 to 60%. Currently, the inactivated vaccine, trivalent or quadrivalent, is recommended annually for all children older than 6 months of age. The live attenuated intranasal vaccine can be an option for children older than 2 years of age without underlying chronic medical conditions if they refuse to receive the inactivated vaccine. However, evidence suggests that this vaccine is less effective.

Although antiviral medications may attenuate the course of influenza when given early, immunoprophylaxis with vaccines is the most effective strategy for the control of influenza infections.

Avian influenza has occurred in epidemics among persons with close contact to live, infected poultry. All children with pneumonia who progressed to ARDS succumbed to the disease.

33.4.2.2 Avian Influenza

Avian influenza viruses do not normally infect species other than birds and pigs. However, in 1997, the first human death from avian influenza occurred in Hong Kong in a 3-year-old with Reye syndrome. Subsequently, an epidemic occurred among humans in Hong Kong with close contact to live, infected poultry. A highly pathogenic H5N1 subtype was isolated. This outbreak was curtailed by the culling of poultry with periodic closings of live bird markets for cleaning. In 2003 re-emergence of the avian H5N1 strain occurred. Through migrating birds, the virus rapidly spread to other countries in Southeast Asia and other parts of the world, including Africa and Europe. As of 2018, 856 human cases have been reported to WHO, with a 52.8% reported mortality. There are only a few proven human-to-human transmissions. Children uniformly present with fever and cough. Symptoms range from typical influenza-like symptoms to conjunctivitis to respiratory disease and failure. Significant laboratory data include leukopenia and thrombocytopenia. All children who developed pneumonia and progressed to ARDS died. Diagnosis remains difficult, as no tests are widely available.

33.4.2.3 Novel H1N1 Influenza A

In April 2009, the Centers for Disease Control confirmed the emergence of a novel influenza A (H1N1) virus with genes from swine viruses of the Eurasian lineage and genes from avian influenza viruses. By June 2009, the first influenza pandemic since 1968 was declared, affecting over 191 countries and territories. In comparison to illnesses with seasonal influenza, the majority of cases occurred in individuals younger than 65 years of age, with nearly half of the cases occurring in children under 18 years of age. Fortunately, the pandemic was less severe than expected and comparable to an average influenza season.

The clinical symptoms can be typical for influenza: fever, sore throat, cough, and muscle aches with the addition of vomiting and diarrhea in children. A wide range of complications were reported ranging from mild-to-moderate (otitis media, sinusitis, myositis, and febrile seizures) to more severe complications, such as myocarditis, rhabdomyolysis, or encephalitis. Severe complications may frequently involve invasive bacterial coinfection (e.g., MRSA) and/or exacerbation of underlying medical conditions in particular asthma. Children who present initially with uncomplicated influenza may have rapidly progressive hypoxemic respiratory failure and multiorgan system dysfunction that is refractory to all therapies (◘ Fig. 33.3).

Of reported H1N1 deaths, approximately 20% were in children. The majority of these children had comorbid asthma, neurodevelopmental conditions, or obesity. An American Academy of Pediatrics Work Group identified children at greatest risk for life-threatening H1N1 influenza disease (► Box 33.1).

Like other strains of influenza, the Center for Disease Control recommended prompt empiric antiviral therapy with oseltamivir for infants, children, and adolescents of any age presenting with suspected or confirmed H1N1 influenza requiring hospitalization, especially with severe, progressive, or complicated illness regardless of length of time from presentation. See above for more details regarding antiviral therapy options. The current trivalent and quadrivalent vaccines now include newer variants of the 2009 H1N1 strain.

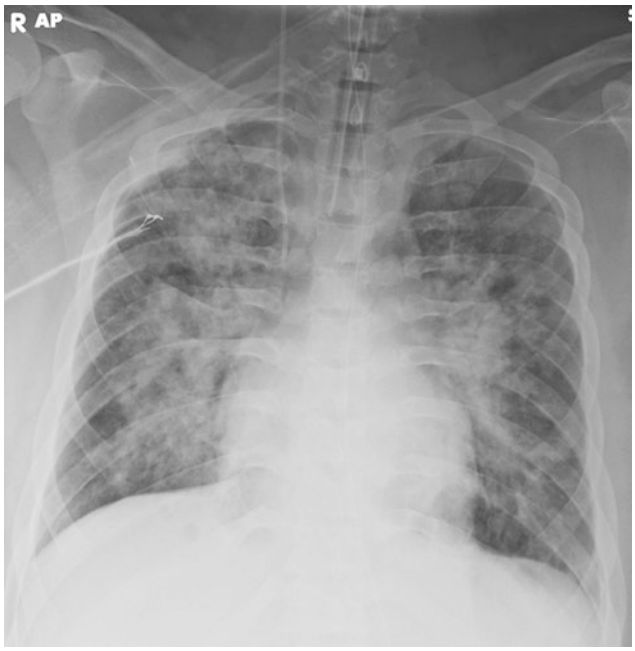


Fig. 33.3 Chest radiograph of a 17-year-old with rapidly progressing hypoxemic respiratory failure secondary to H1N1. (Image provided courtesy of FA Maffei)

Box 33.1 High-Risk Conditions Associated with Life-Threatening H1N1 Infection

1. Neurological disorders, such as epilepsy, cerebral palsy, developmental delay, and neuromuscular disorders
2. Chronic respiratory diseases associated with impaired pulmonary function and/or difficulty handling lung secretions, moderate and especially severe persistent asthma, or technology-dependent children (e.g., those requiring oxygen, tracheostomy, or a ventilator)
3. Primary immunodeficiencies or conditions that require medications or treatments that result in secondary immunodeficiencies
4. Congenital heart disease
5. Metabolic (e.g., mitochondrial) or endocrine disorders, especially if cardiopulmonary function is impaired

Adapted from ► http://www.aap.org/new/swineflu.htm

33.4.2.4 Adenovirus

Adenoviruses have been implicated in 4–10% of pneumonias in children. Adenovirus infections peak between 6 months and 5 years of age. Adenoviruses are grouped into seven species, A through G. Species B, C, and E infect the upper and lower respiratory tracts. Respiratory infection with human adenoviruses is generally mild and self-limited in immunocompetent children. However, there are yearly outbreaks that cause severe respiratory infections and pneu-

Mortality from disseminated adenovirus infections remains high because of multiple organ system involvement.

monia, rarely progressing to ARDS. Outbreaks are generally seen in closed population clusters as in military installations, long-term care facilities and hospitals, and schools and college dorms. Disseminated infections usually occur in immunocompromised patients, especially patients following hematopoietic stem cell transplant or solid organ transplantation. Treatment of disseminated infections is mainly supportive, with mortality rates of 27–45% as the disease often involves multiple organ systems. Cidofovir (CDV) has reportedly reduced viral load and, in some series, improved survival in transplant patients. However, its use is also associated with significant toxicity. Brincidofovir (BCV) is a lipid formulation of CDV with improved oral bioavailability and favorable toxicity profile; however, studies have only shown modest benefit. Immunotherapy research has shown promising results. Survivors may have permanent lung injury often in the form of bronchiolitis obliterans. A live, oral vaccine for adenovirus types IV and VII is approved for use in military populations ages 17 through 50.

33.4.2.5 Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

SARS and MERS rarely affect children, and when it does, morbidity is less, with rare mortality among children with comorbidities.

In 2003 and 2012, two human coronaviruses causing an acute respiratory syndrome emerged. SARS-CoV was first identified in China and is believed to be transmitted to humans from civets that were likely infected from the Chinese horseshoe bat. SARS quickly spread to 29 additional countries causing an atypical pneumonia with 8098 confirmed cases and 774 deaths. The epidemic was contained in 2004 following a highly effective public health response. MERS emerged in the Kingdom of Saudi Arabia. It is hypothesized that bats are the natural reservoir with camels and goats serving as intermediate hosts. MERS has spread to 27 additional countries with 2080 confirmed cases and 722 deaths as of 2017. Human-to-human transmission has been associated with healthcare workers and close contacts of infected persons. Adults (median age 40–50 years) have been mainly infected. Children less than 18 years of age accounted for approximately 5% of those affected with SARS, with a mean age of 12 years. No deaths were reported among children in the 2003 outbreak. In 2014, only 14 of the 701 confirmed cases (2%) were in children. The mean age was 99 months. Nine of these patients were asymptomatic and diagnosed during screening of family contacts; all were healthy. Three children developed mild respiratory symptoms. Two patients with comorbidities developed severe respiratory symptoms and multiorgan dysfunction and died. Following a mean incubation time of 5 days, symptoms developed including fever, chills, cough (occasionally bloody), shortness of breath, myalgia, headache, nausea, vomiting, diarrhea, sore throat, and malaise. Progression to severe disease was more rapid with MERS as compared to SARS, with 7 and 11 days, respectively. Laboratory abnormalities include elevated lactate dehydrogenase and liver enzymes, lymphopenia, and leukopenia. Radiographs of the chest show nonspecific infiltrates. Secondary bacterial infections have occurred. No approved therapeutics are available with clinical management primarily supportive.

33.4.2.6 Hantavirus Cardiopulmonary Syndrome (HCPS)

Hantavirus is rare in infants and school-aged children. No deaths have been reported in children less than 14 years of age.

Hantavirus cardiopulmonary syndrome is a viral zoonotic disease that affects healthy children and adolescents who are exposed to aerosols of rodent excreta. The deer mouse is the main rodent reservoir. Most cases occur in the southwestern United States, but cases have been confirmed in 30 states. HCPS presents with a prodrome of fever, chills, myalgia, headache, and gastrointestinal symptoms. Respiratory compromise requiring supplemental oxygen generally

occurs within 72 h. The disease can progress to acute respiratory distress syndrome. The majority of deaths result from hypoxemia and cardiac dysfunction with marked hypotension and ventricular arrhythmias. In adults, the case fatality rate is approximately 38%. A case series of 13 children aged 10–16 years revealed that 92% of infected children developed HCPS, 33% died, and 67% were critically ill and required mechanical ventilation. Treatment is supportive. Extracorporeal membrane oxygenation was used on two patients, one of whom survived. Laboratory evaluation reveals thrombocytopenia, leukocytosis, and circulating immunoblasts. An elevated prothrombin time of ≥14 s is predictive of severe disease. No deaths were reported in children younger than 14 years of age. Diagnosis can be made by detection of hantavirus-specific immunoglobulin M, hantavirus-specific RNA by polymerase chain reaction, or hantavirus antigen by immunohistochemistry.

33.4.3 Pneumonia in the Immunocompromised Host

Respiratory infections in children with primary or acquired immunodeficiencies requiring intensive care are not uncommon. These infants and children are susceptible to many organisms that are rarely pathogenic in a normal host. Primary immunodeficiencies include abnormalities or deficiencies in immunoglobulins, T and B cells, phagocytes, natural killer cells, and complement. Acquired immunodeficiencies include asplenia, human immunodeficiency virus (HIV) infection, corticosteroid therapy, and immunosuppression used for marrow or solid organ transplants.

Immunocompromised children can present with attenuated signs and symptoms of respiratory infections. In addition to physical examination and chest radiographs, these children often require chest computed tomography to better delineate the extent of disease. Bronchoalveolar lavage, needle aspiration, or lung biopsies might be required to make a definitive diagnosis. Pulmonary specimens should be tested for common bacteria as well as for *Pneumocystis jirovecii*, acid-fast bacilli, *Nocardia*, *Legionella*, *Cryptococcus*, *Aspergillus*, *Candida*, *Histoplasma*, *Coccidioides*, and *Blastomyces*. Viruses such as cytomegalovirus, varicella, herpesvirus, and measles should be considered.

33.4.3.1 *Pneumocystis jirovecii* Pneumonia (PJP)

Pneumocystis jirovecii (formerly known as *Pneumocystis carinii*) is an opportunistic pulmonary pathogen in infants and children with human immunodeficiency virus (HIV) and other primary immunodeficiencies and hematological malignancies, solid organ and bone marrow transplant recipients, and patients on high-dose corticosteroid therapy for inflammatory and collagen-vascular diseases. It is a unicellular organism that exists as a cyst (the diagnostic form). The organism attaches to the type I alveolar cells resulting in an alveolitis characterized by ventilation-perfusion mismatch and decreased pulmonary compliance. If untreated, PCP carries a mortality rate of 25–50% and nearly 100% in the HIV-seropositive child. Fortunately, the incidence has markedly decreased with the administration of chemoprophylactic agents to high-risk patients. Children typically present with fever, tachypnea, nonproductive cough, and hypoxemia with an absence of crackles on auscultation of the chest. Lactate dehydrogenase levels are generally elevated. Bilateral diffuse alveolar infiltrates are seen with initial hilar involvement subsequently spreading to the periphery (◘ Fig. 33.4). Diagnosis is made by demonstrating the organism with dye-based staining in pulmonary tissue, respiratory secretions, or lung fluid or via PCR-based assays. Bronchoalveolar lavage is the most widely used technique to obtain lung fluid

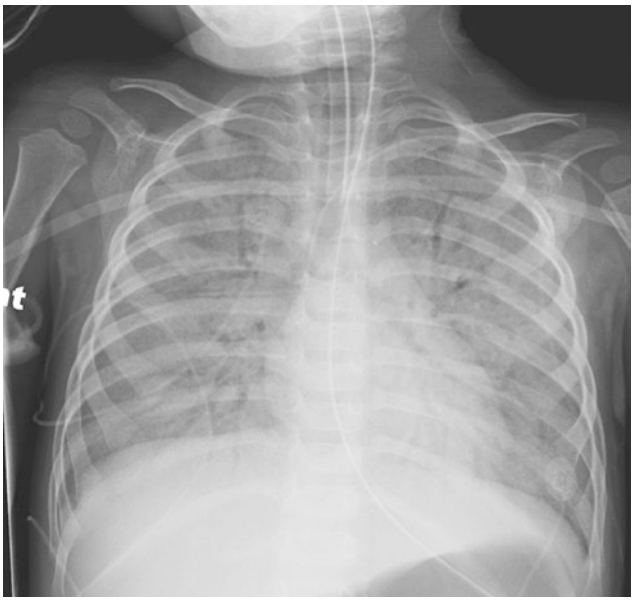


Fig. 33.4 Chest radiograph of severe *Pneumocystis jirovecii* pneumonia in a 13-month-old male with combined immunodeficiency. Note the diffuse alveolar involvement and air bronchograms. (Image provided courtesy of FA Maffei)

for diagnosis. Treatment consists of supportive therapy with supplemental oxygen; ultimately continuous positive airway pressure or mechanical ventilation may be necessary if respiratory failure occurs. Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended initial treatment. In patients who cannot tolerate TMP-SMX, then pentamidine isethionate should be used. Corticosteroids in anti-inflammatory doses as an adjunct to antimicrobial therapy have improved clinical outcomes. Concurrent pulmonary infections were found in 35% of patients, most frequently bacterial or cytomegalovirus pneumonia.

33.5 Diagnosis of Pneumonia

Determination of the etiologic agent in pneumonia is difficult. Fortunately, in most community-acquired pneumonias, identification of the specific causative organism is not critical. However, in children with a complicated course that fails to respond to standard therapies, definitive diagnosis of the etiologic agent is essential. Complete blood counts, inflammatory markers, and chest radiographs do not differentiate the causative agents for pneumonia. Blood cultures are rarely positive outside of the neonatal period with recent studies demonstrating rates of 1.4–3.4%. Despite these low rates, it is still recommended that children admitted for CAP should have blood cultures sent. PCR for diagnosis of respiratory pathogens has become common, and there is some evidence that these tests decrease antibiotic usage as well as chest radiographs. In addition to PCR, rapid antigen tests are available for RSV, rhino−/enterovirus, parainfluenza, influenza, and adenovirus. Nasopharyngeal swabs for viral cultures generally take 7–8 days to become positive, and in one study, 86% of the patients had been discharged prior to the positive results. Older children and adolescents might be able to produce sputum for Gram stain and culture. An adequate specimen should contain more than 25 leukocytes and fewer than 25 squamous epithelial cells per low-power field. In the intubated patient, a

tracheal aspirate can be more easily acquired. However, interpretation of the results of Gram stains and cultures is at times difficult in differentiating colonizing from pathologic organisms. Colonization of the endotracheal tube may occur as early as 12 h but most frequently between 60 and 96 h. The oropharynx becomes colonized within 36 h, the stomach at 36–60 h, and the lower respiratory tract between 60 and 84 h. In addition, a comparison of infectious agents isolated by both tracheal aspirates and bronchoalveolar lavage found only 36% concordance.

Bronchoalveolar lavage (BAL) can be safely used to obtain secretions from the lower airways for Gram stain and culture. It is especially useful in the diagnosis of pneumonia in the immunocompromised child. However, BAL performed directly through the bronchoscope carries a risk of contamination. Non-bronchoscopic double-lumen plugged catheters can be inserted blindly through the endotracheal tube to obtain a specimen. A recent study in 25 patients demonstrated that when the results of blind tracheal aspirate and BAL were compared, only 36% of patients demonstrated the same organisms by both techniques. Transthoracic needle aspirations are performed in some centers with good results. One study reported a diagnostic success rate in 59% of patients. The incidence of pneumothorax was approximately 20%, but none required subsequent placement of a pleural drainage catheter. A lung biopsy is rarely needed to make a definitive diagnosis.

All patients admitted to the hospital for CAP should have a chest radiograph done to describe parenchymal infiltrates and identify complications of pneumonia such as parapneumonic effusion. Routine daily chest radiographs are not recommended; however, if patients fail to improve after 48 h of antibiotics treatments, repeat chest radiography is indicated. If the presence of pleural fluid is not clear on chest radiograph, then chest CT or bedside ultrasound (US) should be considered. Chest US is considered safer due to the lack of ionizing radiation. In addition, US can help to identify simple vs. loculated effusions which may affect treatment decisions.

33.6 Treatment

Supportive treatments with oxygen and intravenous fluids are often standard therapies. As both pneumonia and mechanical ventilation can cause an elevation in antidiuretic hormone levels, careful fluid monitoring is essential to avoid overhydration, excessive lung water, and hyponatremia. Initial antibiotic choices should be empiric and based upon the likely organisms for each age group because of the difficulty in identifying the causative agent. Empiric antibiotics for patients requiring hospital admission were recommended in the 2011 IDSA Guideline for Management of Community Acquired Pneumonia in Infants and Children (■ Table 33.3).

The child's respiratory status including respiratory rate, work of breathing, pulse oximetry, and central nervous system response should be closely monitored. There are several options available for noninvasive respiratory support. High-flow nasal cannula provides heated and humidified air blended with oxygen through a nasal cannula at rates up to 8–10 L/min in infants and 60 L/min in children and adults. This is thought to provide some positive airway pressure, maintain a constant delivered FiO_2, wash out CO_2 from anatomical dead space, improve mucociliary clearance due to humidification, and decrease patients' work of breathing. There is a paucity of data around the use of high-flow nasal cannula in children with community-acquired pneumonia. A recent

Table 33.3 Antibiotic regimen for community-acquired pneumonia

Inpatient All ages	Presumed bacterial infection	Presumed atypical pneumonia	Presumed influenza pneumonia
Fully immunized; local penicillin resistance in invasive strains of pneumococcus is minimal	Ampicillin or penicillin G; alternatives, ceftriaxone or cefotaxime; addition of vancomycin or clindamycin for suspected CA-MRSA	Azithromycin; alternatives, clarithromycin, erythromycin, doxycycline, or levofloxacin (for children who have reached growth maturity and cannot tolerate macrolides)	Oseltamivir or zanamivir
Not fully immunized; local penicillin resistance in invasive strains of pneumococcus is significant	Ceftriaxone or cefotaxime; alternative, levofloxacin; addition of vancomycin or clindamycin for suspected CA-MRSA	As above	As above

Adapted from Bradley (2011)

multicenter RCT demonstrated that among infants with bronchiolitis, those treated with high-flow nasal cannula had significantly lower rates of escalation of care due to treatment failure with no difference in length of stay or duration of oxygen therapy.

Noninvasive BiPAP ventilation can be effective for children with moderate respiratory insufficiency.

Another option for noninvasive respiratory support is bi-level positive airway pressure (BiPAP). BiPAP decreases patients' work of breathing and recruits alveoli resulting in decreased V/Q mismatch. It was effective in children with mild-to-moderate respiratory insufficiency, defined as an A-a gradient >100 and <250 mm Hg or PaO_2/FiO_2 ratio < 200 but >100. There are many options for masks to use with BiPAP including nasal pillows, nasal masks, masks covering the nose and mouth, and full-face masks. Serial evaluation of mask-face contact areas is essential to avoid skin breakdown. Often older children tolerate BiPAP initiation with minimal coaching; however, younger children may require sedation to limit anxiety or agitation with BiPAP.

Children with moderate or severe respiratory insufficiency often require intubation and mechanical ventilation. Children with respiratory failure secondary to pneumonia often require increased positive end-expiratory pressure (PEEP), increased inspiratory time, and aggressive pulmonary toilet to recruit alveoli. For patients requiring high levels of PEEP, adequate sedation is often required to prevent patient/ventilator asynchrony and barotrauma. Spontaneous respirations should be encouraged while on mechanical ventilation, although some patients require the use of neuromuscular blockade to allow mechanical ventilation. Some patients with pneumonia progress to acute respiratory distress syndrome (ARDS). Please see ARDS chapter for definition and lung protective ventilation strategies.

Pneumonias can often be complicated by the development of pleural effusions and empyemas. These occur when the fluid production by the interstitial lung tissue exceeds the maximum pleural lymphatic flow. In addition, direct infection in the pleural space contributes to fluid accumulation and may obstruct lymphatic drainage through the inflammatory response. Parapneumonic effusions often occur from pneumonia as white blood cells and other infectious debris block the lymphatics resulting in elevation of protein in the pleural space, which increases pleural fluid colloid osmotic pressure, and consequent failure of fluid reabsorption. On physical exam, the child has decreased breath sounds over the effusion. In older children, auscultatory percussion changes might be appreciated. Plain chest radiographs can reveal most clinically significant effusions. Ultrasound and chest computed tomograms are useful in determining the volume and quality of the fluid and the presence of loculations. Simple parapneumonic effusions or transudates can also be differentiated from exudates by using the criteria of Light et al. (▶ Box 33.2). The Light criteria misclassify about 25% of transudates as exudates usually in patients receiving diuretics. In these patients, a serum to pleural fluid gradient greater than 3.1 gm/dL is consistent with a transudate. A pleural fluid pH less than 7.2 indicates a complicated effusion that is likely exudative and requires drainage, whereas a pleural fluid pH more than 7.3 suggests that the effusion may be managed with systemic antibiotics alone.

Complicated parapneumonic effusions or empyemas occur when the fluid becomes purulent. During this stage, the effusions undergo a fibrinopurulent stage with many polymorphonuclear leukocytes, bacteria, and cellular debris entering the fluid. Fibrin is deposited over the pleural surfaces and loculations begin to form. The pH and glucose levels fall as the LDH levels rise. If untreated, they often progress to a third organizing stage in which the exudate develops into an inelastic, fibrotic peel that restricts the lung.

Treatment for parapneumonic effusions, as recommended by the 2011 IDSA Guideline for Management of Community Acquired Pneumonia in Infants and Children, is recommended based on the size, degree of respiratory compromise, and whether the fluid is simple or loculated. Small effusions that don't cause a high degree of respiratory compromise may be amenable to treatment with antibiotics alone. Larger effusions that cause a high degree of respiratory compromise will likely require chest tube placement and drainage. Furthermore, loculated fluid collections are unlikely to improve with drainage alone, and both chest tube drainage with fibrinolytics and video-assisted thoracoscopic surgery (VATS) have been found to be effective treatment options. There is inadequate data to recommend one treatment over the other since both interventions have been shown to improve patient outcomes, including resolution of infection and decreased length of stay in comparison to conservative therapy. Fibrinolytic regimens used in children include both tissue plasminogen activator and urokinase. The risks for bleeding are reportedly low, but this therapy requires close monitoring of chest tube drainage. It is also contraindicated in patients with bronchopleural fistulas or in patients who won't tolerate chest tube clamping during instillation. Chest tube and fibrinolytic therapy was effective 80% of the time with similar length of stay and lower costs when compared with early VATS. There was a failure rate of 15–20% in which patients then need to proceed with VATS. VATS was shown in observational studies to have good outcomes in safety and efficacy.

Box 33.2 Light Criteria with Individual Sensitivity and Specificity of Tests to Distinguish Exudative From Transudative Effusions

- Pleural fluid may be classified as exudative, if one or more of the following criteria are met
- Pleural fluid protein divided by serum protein >0.5 (sensitivity 98%, specificity 83%)
- Pleural fluid lactate dehydrogenase (LDH) divided by serum LDH > 0.6 (sensitivity 86%, specificity 84%)
- Pleural fluid LDH is more than two-thirds of the upper limit of normal for serum LDH (sensitivity 82%, specificity 89%)

Adapted from Light (2002)

33.7 Conclusion

Acute pulmonary infections are common diagnoses that require admission to pediatric intensive care units. Understanding the pathophysiology of lower respiratory infections enables the intensivist to tailor therapy to the individual child and pathogen. Early establishment of a specific etiology and the selection of the correct treatment plan directly impacts clinical outcome.

Review Questions

1. *A 3-month-old, former 27-week premature infant with bronchopulmonary dysplasia presents with clinical signs of bronchiolitis. Analysis of nasopharyngeal secretions by polymerase chain reaction testing identifies respiratory syncytial virus. Which of the following therapies have been proven to have a consistent benefit for RSV bronchiolitis?*
   A. Aminophylline
   B. Bronchodilators
   C. Corticosteroids
   D. Ribavirin
   E. Supportive care

2. *Palivizumab is indicated for which of the following children?*
   A. A 5-month-old, former 27-week premature infant who just underwent surgical repair of a large ventricular septal defect who received palivizumab 2 weeks ago
   B. A 9-month-old, former 28-week premature infant with mild bronchopulmonary dysplasia who received palivizumab 2 weeks ago
   C. A 1-month-old, former 36-week premature infant with peripheral pulmonic stenosis who has never received palivizumab
   D. A 2-month-old full-term infant with a urea cycle defect who has never received palivizumab
   E. An 8-month-old, former 25-week premature infant with bronchopulmonary dysplasia who received his fifth dose of palivizumab a month ago

3. *A 5-year-old, unimmunized male with moderately severe asthma requires hospital admission with a 12-h history of fever, cough, and myalgias in the middle of an influenza outbreak. The most appropriate initial management of this child includes which of the following?*
   A. Intravenous peramivir administered after confirming the diagnosis with rapid testing
   B. Intravenous zanamivir administered as soon as possible

C. Oral amantadine administered as soon as possible
D. Oral oseltamivir administered as soon as possible
E. Orally inhaled zanamivir administered after confirming the diagnosis with rapid testing

4. *A 7-year-old presents with a high fever, respiratory distress, and a parapneumonic effusion on chest radiograph. Which of the following findings would MOST likely suggest the need for video-assisted thoracoscopic surgical drainage of this effusion?*
   A. A mediastinal shift away from the effusion.
   B. A pleural fluid pH > 7.3 and glucose >200 mg/dL.
   C. Persistent drainage for more than 5 days from a percutaneously placed thoracentesis catheter.
   D. Less than one-fourth of the hemithorax is opacified on chest x-ray.
   E. The presence of loculations on ultrasound or computer tomography images.

5. *A 4-year-old male presents with acute hypoxemic respiratory failure (PaO_2/FiO_2 ratio = 150), disseminated intravascular coagulation, and renal insufficiency secondary to catecholamine-resistant shock. Rapid antigen testing identifies influenza. In addition to oral oseltamivir, the initial antimicrobial coverage should include which of the following?*
   A. Cefepime
   B. Intravenous immunoglobulin
   C. Intravenous zanamivir
   D. Trimethoprim-sulfamethoxazole
   E. Vancomycin

6. *A 16-year-old male presents with a 3-day history of fever, chills, myalgia, headache, and gastrointestinal symptoms. On clinical exam, he is febrile, tachypneic with scattered crackles, and hypotensive. There is no rash or evidence of animal bite on exam. His initial laboratory results are remarkable for thrombocytopenia, leukocytosis with an increased percentage of circulating immunoblasts, and elevated levels of lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase. His prothrombin time is 16 s. He is admitted and his respiratory status continues to deteriorate ultimately requiring mechanical ventilation. He remains in refractory shock for several days. After an extensive diagnostic work-up, he is diagnosed with hantavirus cardiopulmonary syndrome based on the detection of hantavirus-specific immunoglobulin M. Of the following, which is most likely to be part of his medical history?*
   A. An underlying immunodeficiency
   B. Being a member of the high school wrestling team
   C. Exposure to rodent excrement
   D. Intravenous drug use
   E. Residence in the Southeastern United States

7. *Corticosteroids have the MOST established benefit in which of the following clinical scenarios?*
   A. A 7-week-old infant with severe bronchiolitis secondary to respiratory syncytial virus.
   B. A 6-month-old, unimmunized infant with severe hypoxemia and respiratory failure secondary to pertussis
   C. A 14-year-old female with necrotizing pneumonia secondary to community-acquired methicillin-resistant *Staphylococcus aureus*

D. A 14-month-old with a history of acquired immunodeficiency syndrome and currently in hypoxemic respiratory failure secondary to *Pneumocystis jirovecii* pneumonia (previously called *Pneumocystis carinii* pneumonia)
E. A 16-year-old native American female with severe cardiopulmonary dysfunction secondary to a Hantavirus infection

Answers

1. E
2. A
3. D
4. E
5. E
6. C
7. D

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Sepsis

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Contents

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Learning Objectives

After reading this chapter, one should be able to:

- Discuss the epidemiology (including risk factors) of sepsis in the pediatric population.
- Discuss the inflammatory cascade triggered by infection agents.
- Discuss the cellular responses to systemic infection including the roles of:
  - Inflammatory cells
  - Endothelial cells
  - Cytokines and other mediators
  - Coagulation system
- Understand the clinical signs and symptoms that result from generalized and organ-specific inflammation and injury.
- Understand the role of appropriate empiric antibiotic coverage, adequate fluid resuscitation, and pharmacologic hemodynamic support.
- Discuss the treatment of sepsis, focusing on the underlying rationale for therapies including:
  - Antibiotics
  - Inotropic support
  - Vasoactive agents
  - Corticosteroids
  - Monoclonal antibodies
  - Cytokine inhibitors and analogues
  - Agents targeted to the coagulation system
- Appreciate the role of genetic/epigenetic regulation of this myriad of immunologic and physiologic responses, and speculate on the future directions of basic and applied clinical science research.
- Identify the types of sepsis care bundles and the components of each type of care bundle.

34.1 Introduction

The management of a child with septic shock relies on a comprehensive understanding of the numerous disciplines embodied in the practice of pediatric critical care medicine. The child with septic shock may have simultaneous derangements in the function of virtually every system of the body including cardiovascular, respiratory, immune, renal, coagulation, hepatic, metabolic, and neurologic. The degree to which physiologic alterations are manifest in a given patient is variable and influenced by multiple host and nonhost factors including the developmental stage, the presence of comorbidities, pathogen-related factors, and genetic influences on both the host inflammatory response and the response to pharmacologic agents, all combining to have a profound influence on outcome. The clinician must possess a systematic and multifaceted approach to these critically ill patients. The goal of this chapter is to provide a comprehensive description of the epidemiology, biology, and pathophysiology (at both the cellular and organ level) of sepsis, as well as outline the current principles of managing septic shock at both the individual and institutional level. It will be apparent that optimal management requires a strong working knowledge of cardiovascular physiology, infectious diseases, multiple organ interactions, immunity, coagulation, pharmacology, and the molecular biology of inflammation.

34.2 Definitions

To determine the epidemiology of sepsis, consensus definitions for sepsis and septic shock were first proposed in the 1990s. It was hoped that the development of standard definitions would not only enable accurate characterization of the epidemiology of sepsis but also serve to stratify patients early in the course of sepsis for the purpose of clinical studies aimed at testing novel therapies. Of the early consensus definitions, the most widely used definition of pediatric sepsis/septic shock is based on the 1992 American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference, with adaptations for the pediatric population. The following four definitions resulted from these discussions: *SIRS*, *sepsis*, *septic shock*, and *severe sepsis*. Although there is overlap between some of these terms (particularly between septic shock and severe sepsis), each is intended to define a particular patient population.

Long-standing clinical observations have identified the presence of tachycardia, tachypnea, hyperthermia, and leukocytosis as signs of infection, although these responses may also be present in the absence of any apparent infectious source. As a result, this physiologic response was defined as the systemic inflammatory response syndrome (SIRS). *SIRS* defines a state of inflammation/immune activation in a child and is based on the presence of at least two of the four criteria listed in ▶ Box 34.1. Thus, patients with diverse clinical conditions such as sepsis, pancreatitis, burns, or severe trauma can meet criteria for SIRS. It has been argued that the SIRS definition is nonspecific and that too broad a range of patients are ultimately classified as having SIRS.

Sepsis is defined as a SIRS response which is secondary to an infection, either documented by microbiology cultures or other clinical evidence of infection. *Severe sepsis* is defined by sepsis criteria plus evidence of insufficient end-organ perfusion (▶ Box 34.1). Finally, *septic shock* is defined by sepsis criteria plus hypotension (two distinct measurements <3rd percentile for age) after the administration of at least 20 mL/kg of crystalloid or colloid, in addition to the criteria listed for severe sepsis (▶ Box 34.1).

These criteria have been used extensively for conducting clinical investigations and have proven to be of value despite criticism for lack of both sensitivity and specificity. The latest consensus conference was convened in 2014 by the American College of Critical Care Medicine to update the 2007 guidelines.

The 2014 update for pediatric and neonatal septic shock guidelines continued to be based on the clinical definitions of the 2007 guidelines. However, in 2016 a consensus group comprised of members from the Society of Critical Care Medicine and the European Society of Intensive Care Medicine redefined the definitions for sepsis in adults by publishing the Sepsis-3 criteria. The criteria define sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction is based on an increase in the Sequential Organ Failure Assessment (SOFA) of two points or more. Septic shock is defined as a subset of sepsis with profound circulatory dysfunction. Despite recent studies demonstrating an association with age-adapted SOFA scores and mortality in children, pediatric definitions of sepsis have not changed to rely on SOFA scores. Most recently, the Surviving Sepsis Campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children were published in 2020. For those guidelines, septic shock was defined as severe infection leading to cardiovascular dysfunction (including hypotension, need for treatment with a vasoactive medication, or impaired perfusion) and "sepsis-associated organ dysfunction" as severe infection leading to cardiovascular and/or noncardiovascular organ dysfunction.

Box 34.1 Criteria for SIRS, Severe Sepsis, and Septic Shock

Criteria for SIRS

Patients must present with at least two of the following four criteria:

1. Temperature > 38 °C or < 36 °C (as determined by central temperature)
2. Heart rate > 90th percentile for age
3. Respiratory rate > 90th percentile for age or hyperventilation to $PaCO_2$ < 32 mm Hg
4. White blood cell count >12,000 cells/μL or <4000 cells/μL

Criteria for severe sepsis

Sepsis plus any *one* of the following:

1. Glasgow coma score <15 in the absence of CNS disease
2. Arterial blood lactate >1.6 mmol/L or venous blood lactate >2.2 mmol/L
3. Urine output <1 mL/kg/h for 2 consecutive hours with a urinary catheter in place

Criteria for septic shock

Sepsis with hypotension (two distinct measurements of blood pressure <3rd percentile for age) after administration of 20 mL/kg of crystalloid or colloid, plus any *one* of the following:

1. Requirement for inotropic or vasopressor support (excluding dopamine ≤5 μg/kg/min)
2. Any of the diagnostic criteria for severe sepsis listed above

SIRS is a state of inflammatory/immune activation and is based on the presence of at least two of the four following clinical criteria: temperature >38 °C or <36 °C, heart rate > 90th percentile for age, respiratory rate > 90th percentile for age, or hyperventilation to $PaCO_2$ < 32 mm Hg. The definition attempts to "capture" all patients at risk for the subsequent development of severe sepsis or septic shock.

34.3 Epidemiology

In one of the earliest studies to investigate pediatric sepsis, Proulx analyzed the incidence and outcome of SIRS, sepsis, severe sepsis, and septic shock in a single institution. Over 1000 admissions were analyzed over a 1-year period. SIRS was present in 82% of patients, while 23% had sepsis, 4% had severe sepsis, and 2% had septic shock. The overall mortality for this population was 6% with a majority of deaths occurring in patients with multiple organ dysfunction syndrome (MODS).

An epidemiologic study using discharge International Classification of Disease, 9th revision (ICD-9) codes reviewed hospital records from seven large states representing nearly one-quarter of the US population. While the criteria used for inpatient coding at discharge are not identical to ACCP/SCCM Consensus Conference criteria, the study estimated an incidence of 42,371 cases of severe sepsis in individuals less than 20 years of age (0.6 cases/1000 population). The highest incidence was in neonates (5.2 cases/1000 population), compared to children ages 5–14 who had an incidence of 0.2 cases/1000 population. The overall mortality rate was 10.3% (4364 deaths nationally) consistent with the frequent observation that the mortality rate remains lower than

comparable adult data. The study estimated an annual national healthcare cost of $1.7 billion associated with severe sepsis in children. A follow-up study with the same methodology appeared to show a 13% increase in the absolute number of cases of severe sepsis from 1995 to 1999 with the majority of this increase accounted for by severe sepsis in children less than 1 year of age. The mortality rate had decreased to 9.0% during this time period. A recent systematic review of pediatric and neonatal sepsis estimated the global burden of sepsis to have an incidence of 3 million cases of neonatal sepsis and 1.2 million cases of pediatric sepsis.

Weiss and colleagues performed a point prevalence study at 128 sites in 26 countries to determine the global prevalence of severe sepsis in pediatric intensive care units. Hospital mortality was 25% in the 569 cases of severe sepsis they identified. Interestingly, the mortality did not differ between resource-rich and resource-poor sites. They also identified that 17% of survivors developed a significant morbidity.

Collectively, these data illustrate that sepsis is a major health problem on the basis of incidence, mortality, and healthcare costs. There remains a need for further, well-designed epidemiologic studies of pediatric sepsis. Future studies will enhance our understanding of not only epidemiology but also the impact of new diagnostic and therapeutic approaches resulting from improved design of interventional trials specific to the pediatric population.

34.4 Clinical Presentation

Common clinical manifestations of sepsis include fever or hypothermia, tachypnea, tachycardia, leukocytosis or leukopenia, thrombocytopenia, and change in mental status.

Sepsis is a systemic disease and can impact the functioning of all organ systems. The most common clinical manifestations of sepsis include fever or hypothermia, tachypnea, tachycardia, leukocytosis or leukopenia, thrombocytopenia, and a change in mental status. One of the earliest signs of infection is fever which results from the pyrogenic effect of cytokines, particularly interleukin (IL)-1β and tumor necrosis factor (TNF)-α. Presentation with hypothermia can also occur but is more common in infants.

Children with sepsis may have hemodynamic characteristics that transcend traditional classification. They often have elements of hypovolemia, cardiac dysfunction, and abnormal vascular tone.

One traditional classification of shock states divides this clinical state into three broad categories: hypovolemic, cardiogenic, and distributive shock. The shock associated with sepsis is unique in that all three forms are likely to be present. Hypovolemic shock results from capillary leak, increased insensible losses, and decreased effective blood volume secondary to venodilation. Cardiogenic shock is related to direct myocardial depression, the cause(s) of which remains the focus of investigation. Finally, distributive shock is often apparent as brisk capillary refill, widened pulse pressure, and bounding peripheral pulses and is caused by abnormally decreased systemic vascular resistance from pathologic vasodilation. The particular pattern of these hemodynamic physiologic perturbations manifested by any individual patient can be variable. Some children have increased cardiac output with diminished systemic vascular resistance characteristic of distributive shock or the so-called "warm" shock state. In stark contrast to adults, in which this hemodynamic profile (increased cardiac output/decreased systemic vascular resistance) is most common, children more frequently present with depressed cardiac output and elevated systemic vascular resistance. These patients appear cool with diminished pulses and poor capillary refill that is characteristic of the "cold" shock state. While important to recognize that patients may transition from one state to another, the presence of hypotension is often a late and particularly ominous sign that requires prompt intervention as its presence is associated with increased mortality.

In the septic child, the combination of capillary leak, decreased myocardial function, and the result of fluid resuscitation may result in rapid progression to acute respiratory failure.

Patients with sepsis often present with alterations in their respiratory system, notably tachypnea that reflects a compensatory respiratory alkalosis aimed at neutralizing a metabolic acidosis related to hypoperfusion and anaerobic metabolism. Chest radiographic findings can reveal a small heart in the presence of hypovolemia with few vascular markings. Alternatively, the combination of capillary leak, decreased myocardial function, and the result of fluid resuscitation in some children with sepsis can result in pulmonary edema. Rapid progression to acute respiratory distress syndrome (ARDS) and respiratory failure is not uncommon. All organ systems and ultimately cellular functions are affected by poor perfusion and decreased oxygen delivery related to depressed cardiac and respiratory function. In addition, there may be direct injurious effects of bacterial toxins and circulating cytokines such as triggering of programmed cell death or apoptosis. The neurologic state of a child with sepsis is frequently altered and can range from agitation or irritability to frank obtundation. This depressed mental status can be present even in the absence of meningitis as a manifestation of cerebral hypoperfusion. Skin manifestations are not uncommon and can include petechiae and purpura that are ominous signs of disseminated intravascular coagulation (DIC) and purpura fulminans secondary to meningococcemia. Diffuse erythema secondary to toxic shock syndromes can be present. There is also an increasing appreciation of sepsis-induced microvascular angiopathy contributing to distal skin and organ ischemia. An initial thorough and detailed physical exam provides both important clues to the diagnostic possibilities of pediatric septic shock and the underlying hemodynamic profile. However, serial exams are imperative to follow pathophysiologic changes and to gauge the impact of therapeutic interventions in reversing the manifestations of shock.

34.5 Pathogenesis of Sepsis

Data from both clinical and basic science studies have supported the hypothesis that pathogens and/or their products initiate a host immune response that triggers widespread inflammation causing tissue injury and organ dysfunction. Potential initiating pathogens include gram-negative and gram-positive bacteria, viruses, fungi, and protozoa. In some cases, overwhelming spread of pathogens (e.g., bacteremia) with release of toxins (e.g., endo- or exotoxins) may directly injure the host resulting in organ dysfunction.

The cells of the innate immune system contain cell surface molecules termed pattern-recognition receptors (PRRs). These receptors are capable of recognizing a broad array of conserved structures on a variety of pathogens (so-called pathogen-associated molecular patterns, or PAMPs). Examples of PAMPs include lipopolysaccharide, lipoteichoic acid, viral RNA, and bacterial DNA.

Higher-order organisms have evolved an immune system to eradicate pathogens which has evolved to include two systems: the innate or natural immune system and the acquired or adaptive immune system. The innate immune system is responsible for the highly conserved function of recognizing pathogens and mounting an effector response. It includes a series of molecules located on the cell surface termed pattern-recognition receptors (PRRs) which are capable of recognizing a broad array of conserved structures on a variety of pathogens (so-called pathogen-associated molecular patterns, or PAMPs). Examples of PAMPs include lipopolysaccharide (LPS) on gram-negative bacteria, lipoteichoic acid on gram-positive bacteria, mannans on yeast, double-stranded RNA of RNA viruses, and unmethylated, CpG DNA from bacteria. The effector responses that are regulated by the innate immune system (e.g., phagocytes, complement) are activated immediately upon infection and are designed to rapidly inhibit the replication of microorganisms.

These cell surface PRRs are expressed on most antigen-presenting cells of the innate immune system and represent diverse families of proteins. One group of PRRs, the Toll-like receptors (TLR), has been identified as perhaps the most critical pathogen-recognition receptor family in the context of sepsis biology. Other families of PRRs include the C-type *coll*agenous *lectins* (collectins) that bind to a variety of carbohydrate moieties on cells, bacteria, and viruses. Most members of this family share structural homology to the complement protein C1q and can functionally substitute for C1q in activating the complement cascade. Another family of PRR possesses leucine-rich regions critical for protein-protein interactions that are necessary for immune recognition. Examples of these leucine-rich receptors include CD14, a receptor on the cell surface of macrophages that binds to LPS, and the macrophage scavenger receptor that binds to bacterial cell walls. Unbound circulating PRRs exist and include pentraxins, such as C-reactive protein, an acute-phase reactant synthesized by the liver, and lipopolysaccharide-binding protein (LBP) which binds to LPS to optimize its binding to the CD14/Toll-like receptor cellular complex.

Toll-like receptors (TLR) are pathogen-recognition receptors that have a critical role in sepsis. TLR4 is active in recognition of LPS on gram-negative bacteria, whereas TLR2 is active in the recognition of lipoteichoic acid on gram-positive bacteria.

Another key component of innate immunity is the complement system. The complement system is a complex cascade of proteins that possesses a broad array of anti-pathogen activities including opsonization (C3), neutrophil chemotaxis (C5a), perforating cytotoxicity (C6–9, MAC complex), and the ability to bind to and directly lyse viruses (C1). An in-depth discussion of the role of complement in the response to infection is beyond the scope of this chapter but has been recently summarized (Heesterbeek et al. 2018). In summary, the host possesses a ubiquitous and diverse set of pathogen-recognition receptors which function to protect the host from infectious challenges, but at the expense of triggering powerful effector responses.

Paramount to effector responses of the innate immune system is a proinflammatory action of numerous cytokines and chemokines. These biologically active proteins are critical to the activation and recruitment of cellular components of the adaptive immune system. While necessary for pathogen clearance, this acute, proinflammatory immune response must also ultimately subside in order to reestablish homeostasis and avoid cellular and tissue damage. A key pathophysiologic feature of sepsis is that this immune response often appears to become unregulated resulting in an overwhelming proinflammatory response and host auto-destruction. This characteristic systemic inflammatory response seen frequently in response to infection can also be observed in association with noninfectious triggers (e.g., trauma, burns, pancreatitis, cardiopulmonary bypass).

A hallmark of sepsis is an immune response that appears to become unregulated resulting in an overwhelming proinflammatory response and host auto-destruction. This characteristic systemic inflammatory response is seen frequently in response to infection but can also be observed in association with noninfectious triggers (e.g., trauma, burns, pancreatitis, cardiopulmonary bypass).

34.5.1 Inflammatory Cascade of Sepsis

LPS Recognition Recent epidemiologic surveys of the causative agents of sepsis have indicated an increase in the incidence of gram-positive organisms such that there is a roughly equivalent prevalence between these and gram-negative organisms. Historically, sepsis research has focused on the role of gram-negative bacteria in evoking a pathologic response. The structure of endotoxin consists of three domains: an outer polysaccharide hydrophilic chain which determines the O-antigenicity, an acidic core region, and a lipid-rich region. Gram-negative organisms possess endotoxins with variable repeats of mono- and heteropolysaccharides with complex side chain structure to provide a basis for distinct antigenicity. The O-region is linked via an acidic core to the lipid A region that is highly conserved and responsible for much of the toxicity attributed to intact LPS.

A series of seminal observations have determined the molecular mechanisms by which the classic PAMP, LPS, initiates a proinflammatory response. First, a strain of LPS-resistant mice, the C3H/HeJ strain, was identified, and its resistance was found to be attributed to a single genetic mutation. Second, it was demonstrated that the lethal effects of endotoxin could be conferred by transfer of hematopoietic cells. Endotoxin-tolerant mice could be rendered LPS-sensitive after reconstitution with hematopoietic cells derived from the monocyte/macrophage lineage from an LPS-sensitive strain. Third, stimulation of monocyte-derived cells with endotoxin resulted in production of several cytokines and chemokines critical to the systemic inflammatory response. Among these, TNF and IL-1β were shown to be critical initiators of the septic response and could in fact mimic the endotoxin response. Finally, the elucidation of the LPS receptor assisted the identification of those signal transduction pathways by which endotoxin triggers inflammatory gene expression.

LPS Receptor Membrane-bound CD14 was found to be required for LPS signaling. However, it lacked a transmembrane extension required for cytoplasmic signaling indicating the presence of additional components of the receptor complex. Investigators working with *Drosophila* had identified a gene, Toll, which was responsible for dorsoventral polarization in embryonic development. When Toll was functionally mutated, it was demonstrated to play a key role in host defense against *Aspergillus fumigatus*. Homology between the Toll-like receptors and the mammalian IL-1 family of receptors was discovered and provided additional evidence that this family was crucial to the human innate immune response. Finally, it was determined that the C3H/HeJ mouse strain which is hyporesponsive to LPS possessed a mutation in Toll-like receptor 4 (TLR4), providing further evidence that this receptor was necessary for LPS signaling. TLR4 is one of ten mammalian Toll-like receptors that have been cloned to date, each being activated by a specific set of ligands. Since these discoveries, other members of the LPS-receptor complex have been elucidated and include both MD-2 and MyD88. It is also known that circulating LPS-binding protein (LBP) facilitates LPS binding to the cell surface receptor complex. Together these components are able to "sense" LPS at the cell surface and transmit this signal via a series of complex pathways. Similarly, the products of gram-positive organisms, notably the cell wall component lipoteichoic acid, activate cell activation through the related Toll-like receptor 2 (TLR2).

34.5.2 Signal Transduction Pathways

Nuclear factor-κB (NF-κβ) and the mitogen-activated protein kinase (MAPK) pathways play a prominent role in regulating the expression of a number of inflammatory gene products key to propagating the septic response.

After engagement of cell surface receptors (e.g., TLR2 and TLR4), several important signal transduction pathways are activated that elicit a number of transcriptional factors responsible for inflammatory gene expression. Among these, the nuclear factor-κB (NF-κβ) and the mitogen-activated protein kinase (MAPK) pathways play a prominent role in regulating the expression of a number of inflammatory gene products key to propagating the septic response. In the case of NF-κB, stimulation of the LPS receptor causes phosphorylation of the inhibitor of κB kinases (IκK) which in turn phosphorylates the intracellular inhibitor of NF-κB, I kappa B (IκB). Upon phosphorylation, IκB undergoes poly-ubiquination followed by proteosomal degradation. The removal of IκB effectively unmasks a nuclear translocation sequence on NF-κB enabling it to proceed into the nucleus to bind to NF-κB consensus sequences present on the promoter regions of many inflammatory genes: cytokines including TNF, chemokines including IL-8, adhesion molecules including E-selectin, and oth-

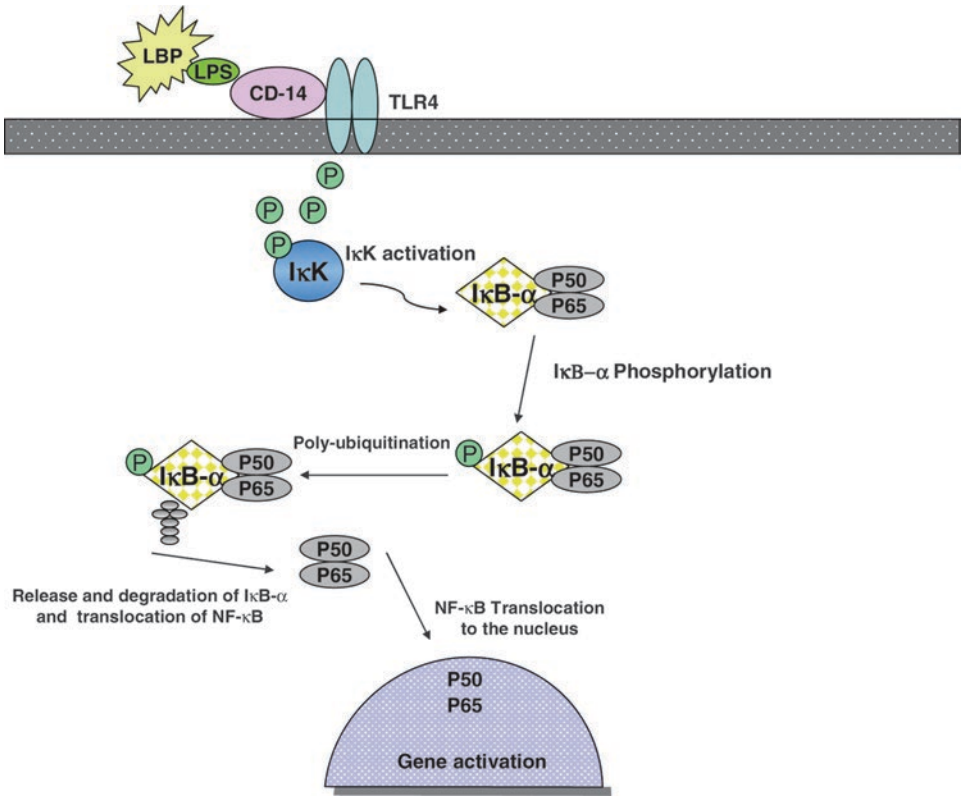

Fig. 34.1 Pathway of LPS-induced activation of the NF-kB pathway resulting in inflammatory gene expression. LPS lipopolysaccharide, LBP LPS-binding protein, TLR4 Toll-like receptor 4, NF-kB nuclear factor kappa-B (transcriptional activating heterodimeric complex), IkB-a inhibitor of kappa B-alpha, IkK I kappa B kinase complex, P phosphorylation

ers such as inducible nitric oxide synthase (iNOS) (Fig. 34.1). The role of NF-κB in sepsis is supported by studies demonstrating that survivors and non-survivors of sepsis are distinguishable on the basis of NF-κB-binding activity in peripheral blood mononuclear cells. In addition, in sepsis-induced ARDS, increased activation of NF-κB in macrophages obtained by bronchoalveolar lavage (BAL) is found in ARDS patients when compared to intensive care unit (ICU) controls.

To a similar degree, the MAPK signaling pathways are important in mediating the septic response. Three MAPK pathways exist: p38 protein kinase, extracellular-regulated protein kinase (ERK), and c-Jun N-terminal kinase (JNK). Evidence exists for the role of each of these signaling pathways in sepsis. TNF production by neutrophils and macrophages is dependent on p38 activation. LPS stimulation of monocytes activates JNK with downstream activation of activating protein-1 (AP-1) and subsequent IL-1β production. LPS induction of TNF is in part dependent on ERK pathway activation. Together, these two pathways, NF-κB and MAPKs, appear to be critical to the propagation of signals from the cell surface to the nucleus where expression of inflammatory gene products occurs. As such, these pathways remain valid targets for future strategies in modulating the septic response.

34.5.3 Principal Gene Products/Mediators of the Septic Response

While numerous proteins have been found to play a role in the septic response, a full review of each protein's function is beyond the scope of this study guide. Instead, we aim to highlight some known principal mediators in this cascade.

34.5.4 Tumor Necrosis Factor-α

TNF-α possesses numerous functions in inflammation such as inducing adhesion molecules and chemokines that facilitate leukocyte-endothelial cell adhesion and inducing nitric oxide synthase (iNOS) which mediates pathologic vasodilation. TNF-α also upregulates tissue factor and inhibits protein C to create a pathologic procoagulant state in the vasculature. Clinically, levels of TNF-α correlate with mortality, with the development of shock and purpura fulminans, and with the development of sepsis-induced ARDS and shock.

Evidence that TNF-α mediates the septic response stems from numerous observations: it is produced by hematopoietic cells, its expression is temporally related to the development of septic shock, recombinant TNF-α induces experimental septic shock in animals, and passive immunization against TNF-α attenuates endotoxin-mediated responses. TNF-α displays numerous functions in inflammation such as driving adhesion molecule and chemokine expression to facilitate leukocyte-endothelial cell adhesion, upregulating tissue factor and inhibition of protein C to create a pathologic procoagulant state in the vasculature, and inducing nitric oxide synthase (iNOS) which mediates pathologic vasodilation. In human studies, levels of TNF-α have been found to correlate with mortality, with the development of shock and purpura fulminans, and with the development of sepsis-induced ARDS and shock.

34.5.5 Interleukin-1β

The name, IL-1, is now used to describe the family of proteins including two agonists (IL-1α and IL-1β) and one antagonist, the IL-1 receptor antagonist protein (IL-1Ra). IL-1β, which is secreted, mediates much of the systemic effects attributed to IL-1 release in sepsis. Synthesized as a propeptide, IL-1β requires proteolytic cleavage by the IL-1-converting enzyme (ICE) to become bioactive. IL-1β utilizes the 80-kDa type I receptor which is associated with a number of adapter proteins (e.g., MyD88, TNF receptor-associated factor 6 (TRAF6), and interleukin-1 receptor-associated kinase (IRAK)) to propagate signals through both the NF-κB and AP-1 pathways. IL-1β infusion elicits fever, hypotension, and leukocytic infiltration to the lungs. In a manner similar to TNF-α, IL-1 stimulates monocyte activation and phagocytosis, increases adhesion molecule expression, and increases tissue factor expression while inhibiting thrombomodulin secretion, thereby creating a procoagulant state. When detected in the circulation of septic patients, IL-1β levels also correlate with mortality. Of note, the IL-1Ra is a circulating inhibitor of IL-1β that binds to the IL-1 receptor without initiating a signal. The expression of IL-1Ra has been found to follow peak expression of IL-1β. It is speculated that IL-1Ra is an endogenous regulator of IL-1β effects. However, in clinical trials, IL-1Ra infusion failed to improve mortality in sepsis.

34.5.6 Adhesion Molecules

Furthering our molecular understanding of sepsis-induced organ dysfunction was the identification of the "leukocyte-endothelial cell adhesion cascade." This cascade is characterized by cytokine activation of the selectin family of adhesion molecules (e.g., E-selectin) on the endothelium which initiate a process of neutrophil "rolling" via interaction with sialylated moieties constitutively present on circulating neutrophils. Activation of the "rolling" neutrophil results in both increased expression and activation of the integrins which in turn bind to intercellular adhesion molecule (ICAM)-1 that is upregulated on the endothelial cell surface by TNF-α and IL-1β. This integrin-ICAM-1 interaction mediates firm adhesion of the neutrophil to the endothelial cell surface.

Finally, in response to various chemotactic cytokines or chemokines, neutrophils migrate to the site of inflammation. Release of both oxygen- and nitrogen-based radical species and proteases by the neutrophils may ultimately contribute to cellular injury and organ dysfunction.

34.5.7 Nitric Oxide

Nitric oxide (NO) is responsible for endothelium-derived relaxation of blood vessels. Three isoforms of nitric oxide synthase are responsible for production of NO: type I, a neuronal isoform (nNOS); type II, an inducible isoform (iNOS); and type III, a constitutive, endothelial isoform (eNOS). TNF-α and IL-1β are capable of inducing iNOS, and increased levels of circulating stable by-products of NO are found in both septic adults and children who simultaneously display low systemic vascular tone. This supports the hypothesis that NO plays a principal role in septic shock via pathologic vasodilation. It has also been suggested that TNF-α and IL-1β may be the so-called myocardial depressant factors by increasing circulating NO through induction of iNOS; however, it is not clear that NO is the exclusive mediator of these effects. In light of the evidence supporting the role of NO in septic shock, clinical trials employing NO synthesis inhibitors in septic shock were initiated. Although early clinical reports and small studies reported that NOS inhibitors could significantly improve blood pressure, this was at the expense of decreasing cardiac output secondary to increased afterload. Given that decreased cardiac output and elevated systemic vascular resistance is not an uncommon hemodynamic profile in pediatric septic shock, it is not clear that NOS inhibitors will have a therapeutic role in pediatric (or adult) sepsis in the future.

34.5.8 Putative Role of "Late" Mediators in the Pathogenesis of Sepsis

Studies employing agents directed against the early mediators of the septic response have been mostly ineffectual. This has led to the hypothesis that additional molecules with delayed kinetics of expression may influence the outcome in sepsis. As an example, it was observed that LPS-challenged mice often die long after peak expressions of TNF-α and IL-1β suggesting that late-acting proteins may contribute to endotoxin-induced mortality. Investigators searching for late expressed proteins identified a member of the high mobility group (HMG)-1 nonhistone chromosomal protein family in conditioned media 16 h after LPS stimulation of macrophages. This protein renamed HMGB1 is a known ligand for the receptor for advanced glycation end products (RAGE). The RAGE receptor is expressed on monocytes and vascular smooth muscle. Binding by HMGB1 activates both the NF-κB and MAPK pathways. Increased expression of HMGB1 was found in endotoxemic mice and in critically ill patients with surgical sepsis where increased levels correlated with non-survival. In animal models, the blockade of HMGB1 can inhibit the inflammation associated with endotoxemia, cecal ligation, and puncture and LPS-triggered acute lung injury. Identification of HMGB1 and similar "late" mediators may provide a broader therapeutic window for successful immunomodulating therapy in sepsis.

34.5.9 Role of Host Mediators in the Resolution of Sepsis

An absence in the decline of proinflammatory mediators such as TNF-α and IL-6 over the course of sepsis is an associated risk factor for mortality.

Monocyte activation results not only in production of proinflammatory cytokines but also expression of a number of endogenous anti-inflammatory cytokines including soluble TNF receptors, the IL-1Ra, and additional anti-inflammatory cytokines, such as IL-10 and TGF-β.

Important anti-inflammatory molecules include IL-10, IL-1Ra, and soluble TNF receptors. IL-10 inhibits expression of proinflammatory cytokines known to contribute to sepsis, as well as important chemokines, including IL-8. In addition, IL-10 increases expression of other anti-inflammatory molecules such as IL-1Ra and soluble TNF receptors.

Regulatory processes and mediators exist for the purpose of modulation and eventual resolution of inflammation and the septic response. The absence of a decline in proinflammatory mediators such as TNF-α and IL-6 over the course of sepsis is an associated risk factor for mortality. Monocyte activation results not only in production of proinflammatory cytokines but also in the expression of a number of endogenous cytokine antagonists including soluble TNF receptors, the IL-1Ra, and additional anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β (TGF-β). IL-10 has multiple anti-inflammatory properties including inhibition of cytokine production from activated monocytes. IL-10 inhibits expression of those cytokines known to contribute to sepsis, as well as important chemokines, including IL-8. In addition, IL-10 increases expression of other anti-inflammatory molecules such as IL-1Ra and soluble TNF receptors. Exogenous administration of IL-10 in various experimental models has been used in an attempt to decrease inflammatory cytokines and diminish organ injury. Human studies found that patients who did not survive ARDS had lower levels of IL-10 in their BAL fluid compared to survivors. Furthermore, the inability to increase IL-10 in response to meningococcal infection was associated with increased mortality. Thus, IL-10 and additional regulatory cytokines (e.g., TGF-β, IL-13) possess a number of anti-inflammatory properties and are important contributors to the endogenous regulation of the acute septic response.

34.5.10 Role of the Coagulation Cascade in Sepsis

AT-III inhibits thrombin by forming thrombin-antithrombin (TAT) complexes. AT-III is decreased in sepsis due to degradation by elastases from activated neutrophils, dilution secondary to volume resuscitation, and impaired hepatic synthesis. Despite a correlation between low AT-III levels and mortality in patients with sepsis, replacement trials of AT-III have failed to demonstrate a significant effect on improving mortality.

The administration of activated protein C was associated with a statistically significant reduction in 28-day mortality in septic adults. However, a recent pediatric study was stopped after an interim analysis revealed that APC administration was highly unlikely to show improvement in outcome.

Dysregulation of the coagulation cascade occurs in sepsis as reflected by activation of procoagulant pathways, consumption of clotting factors, alterations in fibrinolysis, and reduced anticoagulant activity (◘ Fig. 34.2). A common hematologic alteration in sepsis is the development of disseminated intravascular coagulation (DIC) (▶ Chap. 38) which is an acquired state of activation of coagulation and intravascular fibrin formation resulting in vascular thrombosis. In addition to proinflammatory cytokines, tissue factor (TF) activation also plays a prominent role in activating the coagulation cascade, initiating fibrin formation, and contributing to the development of DIC. Concurrent with enhanced production of fibrin, there is decreased fibrinolysis related to increased plasminogen activator inhibitor type I (PAI-1), as well as dysfunction and/or depletion of antithrombin III (AT-III), protein C, protein S, and tissue factor pathway inhibitor (TFPI). AT-III which inhibits thrombin by forming thrombin-antithrombin (TAT) complexes is decreased in sepsis related to degradation by elastases from activated neutrophils, dilution secondary to volume resuscitation, and impaired hepatic synthesis. Despite a correlation between low AT-III levels and mortality in patients with sepsis, replacement trials of AT-III have failed to demonstrate a significant effect on improving mortality.

Protein C is also noted to be depleted among patients with sepsis and septic shock. Regulation of activation of protein C to activated protein C (APC) in the coagulation cascade is mediated in a complex manner and will not be discussed here. APC, upon dissociation from its receptor, binds to its cofactor, protein S, to subsequently inactivate factors Va or VIIIa, thus playing a key role in inhibiting coagulation. It is both antithrombotic and profibrinolytic. APC also possesses anti-inflammatory activity. In models of endotoxemia, APC infusion decreases cytokine production and attenuates neutrophil activation. These anti-inflammatory effects appear to be independent of APC's anti-

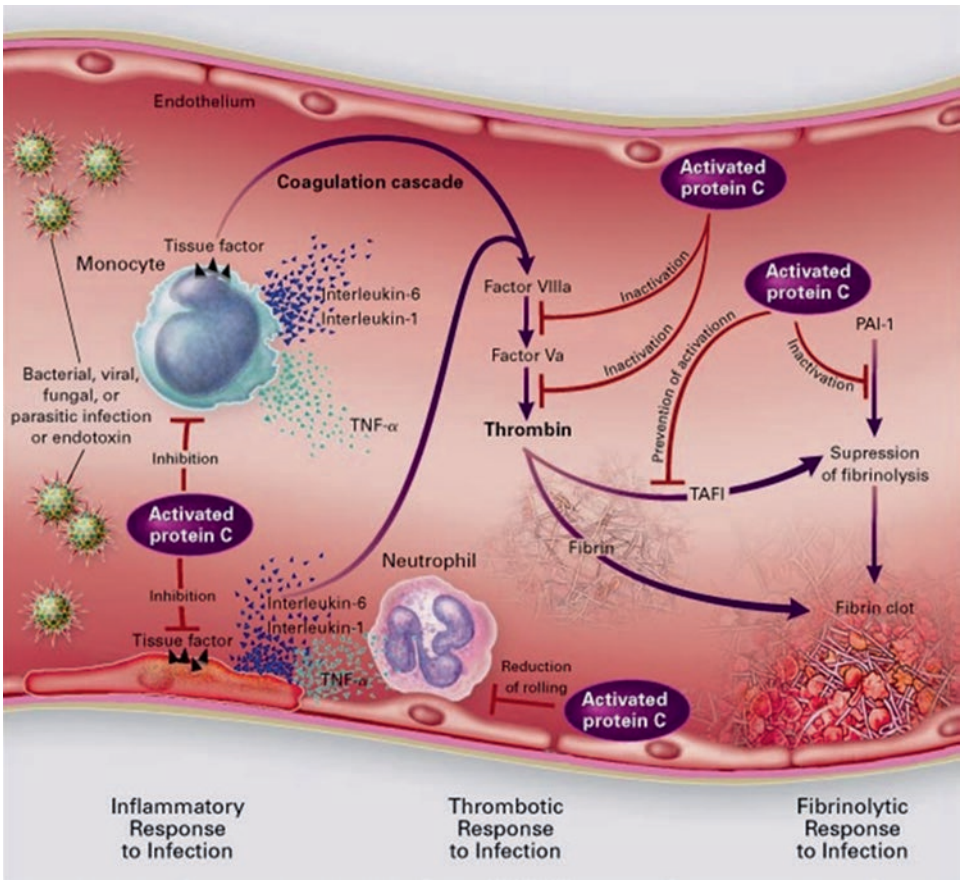

Fig. 34.2 The coagulation cascade in sepsis. (Reprinted with permission from Bernard et al. 2001)

coagulant effect. Following these encouraging preclinical studies, clinical trials examining the effect of APC on mortality from sepsis were commenced culminating in the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial. In this study, APC was associated with a statistically significant reduction in 28-day mortality in septic adults. However, the pediatric study (RESOLVE) was stopped after an interim analysis revealed that APC administration was highly unlikely to show improvement in outcome. Additionally, APC administration was associated with a more than twofold increase in the incidence of central nervous system hemorrhage compared to placebo (4.6% vs 2.1%, $p = 0.13$), particularly in children less than 60 days although the difference did not reach statistical difference.

34.5.11 Genetic Regulation of the Septic Response

It is not uncommon to observe that patients exposed to seemingly identical pathogen insults display strikingly different pathophysiology and outcomes. It is believed that genetic differences among hosts are at least in part responsible for this variability in septic responses. As mentioned previously, the insensitivity to LPS in the C3H/HeJ mouse line was mediated by a mutation in the coding sequence for TLR4. Similar findings of an attenuated response to pathogen stimulation have now been reported in patients with mutations in both the TLR4 and TLR2 gene. The polymorphism in TLR2 appears to confer an increased predisposition to severe gram-positive bacterial infections. More recently, a polymorphism within the CD14 promoter gene (C to T transition at base pair −159) was identified with a particular genotype overrepresented

among septic shock patients compared to healthy controls. Among the septic patients, the presence of this genotype also was associated with a significantly higher mortality (71% versus 48%). These studies support the concept that genetic alterations in those genes known to participate in the septic response affect the host immune response and the likelihood of survival. For a more complete review of the numerous examples of genetic alterations in key inflammatory genes, the reader is directed to the suggested readings.

34.6 Treatment Strategies

34.6.1 Overview

Treatment of sepsis involves four important components: initial resuscitation, elimination of pathogen, maintenance of oxygen delivery, and carefully directed regulation of the inflammatory response.

As the cellular response to sepsis has become better understood, the approach to treatment of sepsis has become broader. The treatment of sepsis involves four important components: initial resuscitation, elimination of pathogen, maintenance of oxygen delivery, and carefully directed regulation of the inflammatory response. As reviewed above, sepsis is an immunologically complex response to an invasive pathogen necessitating tight physiologic regulation in order to eradicate the organism while maintaining cellular and organ homeostasis. In cases where the immunologic and inflammatory responses continue to escalate, numerous pathways are altered and may ultimately prove amenable to immunomodulating therapy, but this approach has been unsuccessful to date.

34.6.2 Initial Resuscitation

The initial priority in the treatment of the septic child is respiratory and cardiovascular stabilization. The primary goals of therapy in those initial hours following clinical presentation are to maintain oxygenation and ventilation, achieve normal perfusion and blood pressure, and reestablish appropriate urine output for age. Children with sepsis may have altered mental status which, if profound, raises concern about the ability to protect the airway. Tachypnea associated with a primary or compensatory respiratory alkalosis is commonly present. The combination of increased lung vascular permeability and aggressive fluid resuscitation to restore intravascular volume and maintain blood pressure may contribute to the subsequent development of pulmonary edema. In children with lung edema, the related changes in lung compliance and loss of functional residual capacity can dramatically increase the work of breathing ultimately necessitating tracheal intubation and mechanical ventilatory support. Arterial blood gas analysis may reveal hypoxemia and metabolic acidosis; however, the decision to provide mechanical ventilatory support should not be based solely on laboratory findings. The presence of increased work of breathing, hypoventilation, and obtundation are all indications for instituting mechanical ventilatory support which holds additional benefit in decreasing the overall oxygen consumption, especially when combined with sedation and paralysis. It should be stated, however, that children with warm shock can commonly be managed without endotracheal intubation as long as they are not obtunded or fluid overloaded. Disorientation or lethargy with intact responsiveness does not require placement of an artificial airway as many institutions manage these patients without intubation. The work of breathing associated with hyperventilation in the absence of pulmonary edema is not clinically significant. Furthermore, there is no evidence that decreasing the work of breathing in the presence of distributive shock will result in redistribution of nutrient flow to vital organs, the very nature of distributive shock. However, it is more common for infants to present with cardiac

dysfunction and pulmonary edema or seriously altered mental status requiring endotracheal intubation and mechanical ventilation. Correction of intravascular volume depletion should be made prior to the institution of positive pressure ventilation. The decrease in venous return after the initiation of positive pressure ventilation may lead to further hemodynamic compromise in the child with intravascular volume depletion. Caution should also be taken in choosing sedative agents for intubation, using agents that have the least impact on tenuous hemodynamics (e.g., ketamine). Following intubation, attention must be paid to matching the mechanically provided minute ventilation to that which was present during spontaneous respiratory effort so that respiratory compensation of acidemia is preserved. If it is deemed that positive pressure ventilation is not needed, supplemental oxygen should be provided to maintain normal oxygen saturations.

With regard to fluid status, septic children have decreased effective intravascular volume related to a number of causes. Poor oral intake of fluid for a period of time prior to clinical presentation is common. Increased vascular permeability leads to intravascular volume loss due to extravasation of fluid from the vascular space to the so-called third space. Finally, the NO-mediated vasodilation reviewed above increases vascular capacitance, thereby decreasing the effective circulating volume. Thus, when sepsis is suspected, it is imperative to expeditiously achieve vascular access and initiate fluid resuscitation with 20 mL/kg of isotonic fluid as quickly as possible. While debate continues as to the most effective fluid for resuscitation, no pediatric literature exists to support colloid over crystalloid, the latter of which was recently demonstrated to be equally effective in a large adult ICU trial. There is some support for using colloid fluid in patients with a narrow pulse pressure; however, this practice is not supported by any large, well-designed clinical studies.

While following the clinical exam for signs of intravascular volume overload (new onset of rales, increased work of breathing, development of a gallop, or hepatomegaly), fluid should be administered quickly with the goal of monitoring heart rate response, blood pressure, urine output, capillary refill time, and level of consciousness. Initial fluid resuscitation of the child with septic shock commonly requires a volume of up to or greater than 60 mL/kg in the first hour, and one retrospective study demonstrated an increased survival in children given fluid volumes of 40 mL/kg or more within the first hour. The ACCM Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock recommend that the child with septic shock be repeatedly examined for the development of "rales, gallop rhythm, hepatomegaly, and increased work of breathing" during volume loading and that in the absence of such findings, volumes up to 200 mL/kg can be administered in the first hour. The 2020 SCCM/ESICM Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-associated Organ Dysfunction in Children suggest "administering up to 40–60 mL/kg in bolus fluid (10–20 mL/kg per bolus) over the first hour, titrated to clinical markers of cardiac output and discontinued if signs of fluid overload develop" if access to an intensive care unit is available.

Adequate volume resuscitation of the child with septic shock commonly requires a volume of up to or greater than 60 mL/kg in the first hour.

Despite ongoing fluid resuscitation, hypotension and inadequate organ perfusion may persist requiring the initiation of inotropes and/or vasopressors. In children, vasoactive medicines should only be given in addition to fluid resuscitation. However, consensus guidelines recommend that vasoactive infusions may be necessary in some cases to sustain perfusion pressure even when hypovolemia is not yet resolved. Dopamine has long been the most common first-choice agent selected for hemodynamic support in those patients with fluid-refractory shock. Dopamine provides inotropic support at lower concentrations; however, it is often necessary to increase it to higher doses that provide vasopressor activity (up to 20 μg/kg/min) to maintain adequate tissue perfusion. The current

Appropriate endpoints of sepsis resuscitation include capillary refill time less than 2 s, normal peripheral pulses, warm extremities, urine output greater than 0.5 mL/kg/h, improved mentation, resolving acidemia, and decreasing serum lactate.

Surviving Sepsis Guidelines suggest using epinephrine or norepinephrine instead of dopamine as the first-line vasoactive infusion although a formal recommendation could not be issued. For example, if hemodynamic instability is related to low cardiac output from direct cardio-depressant effects, then increased inotropy from dobutamine or low-dose epinephrine may be indicated. If hypotension persists secondary to decreased vascular tone, then agents such as epinephrine and norepinephrine dosed in the alpha agonist range should be considered. Finally, in children who demonstrate low cardiac output and/or increased afterload from vasoconstriction (i.e., increased systemic vascular resistance), agents with primarily inotropic or vasodilator function including milrinone, dobutamine, or short-acting nitrovasodilators can be considered in the fluid-resuscitated, normotensive child. As in evaluating the adequacy of fluid resuscitation, similar clinical parameters should be followed in titrating vasoactive medications. Appropriate endpoints include capillary refill time less than 2 s, normal peripheral pulses, warm extremities, urine output greater than 0.5 mL/kg/h, improved mentation, resolving acidemia, and decreasing serum lactate.

34.6.3 Invasive Monitoring

Although frequent bedside examination remains integral to the care of the child in septic shock, an additional task in the initial resuscitation phase is placement of appropriate and necessary vascular access and monitors. Central venous access is a necessity for the child with fluid-refractory shock to provide for delivery of vasoactive medicines and large volumes of fluid. These catheters can be useful for following the central venous pressure (CVP) during fluid administration. Finally, when the tip is located in the superior vena cava (SVC), blood sampling can provide an approximate measure of the mixed venous oxygen saturation which has been validated as a critical target in adult shock resuscitation. The decision regarding the access site for a central venous catheter is dictated by a number of mitigating factors such as the experience level of the operator and the presence of coagulopathy. Femoral catheters, in the absence of abdominal pathology, can be used to estimate CVP with good correlation. The CVP measured in the abdominal inferior vena cava must be assessed carefully as a low CVP can be a reliable indicator of hypovolemia. However, a normal or high CVP in the presence of abdominal distention does not automatically exclude the presence of hypovolemia. Multiple adult studies have demonstrated that even an accurate intrathoracic CVP may be a poor approximation of left ventricular end-diastolic pressure and volume. The CVP can be elevated despite the presence of hypovolemia if pulmonary hypertension, right ventricular dysfunction with poor diastolic compliance, tricuspid regurgitation, cardiac tamponade, or an intracardiac left-to-right shunt exists. Although precise determination of the true mixed venous saturation requires the presence of a pulmonary artery catheter, the approximations derived from the SVC saturation have proven a useful target in septic adults. In contrast, because of differences in oxygen extraction between the upper extremities, abdomen, and lower extremities, venous oxygen saturations from a low-lying femoral line do not accurately correlate with those measured in the pulmonary artery. Consensus guidelines recommend therapeutic endpoints of superior vena cava oxygen saturation >70% or mixed venous (pulmonary artery) oxygen saturation >65%.

Placement of an intra-arterial catheter provides continuous monitoring of systemic blood pressure, pulse pressure, and hemodynamic variation with respiration, as well as a means for drawing arterial blood gases, lactate levels, and additional laboratory studies. The arterial blood also provides the most accu-

rate measure of arterial oxygen content and can be used to both assess the function of the lungs and to maximize oxygen delivery. In the ventilated patient, variation in the amplitude of the arterial waveform has been found to correlate closely with intravascular volume status (see also ▶ Chap. 16). Systolic pressure variation (SPV), also referred to as "reverse pulsus paradoxus," is the variation in beat-to-beat amplitude of the arterial pulse during positive pressure ventilation. A single positive pressure breath normally affects the arterial pressure in a biphasic manner. The initial response to a positive pressure breath is to "squeeze" pulmonary vascular blood into the left atrium (the opposite, "pooling" of blood, occurs with negative pressure inspiration) leading to a rise in systolic pressure. In addition, positive intrathoracic pressure reduces the afterload on the left ventricle by virtue of the pressure gradient from the thorax outward further augmenting this early rise in arterial pressure. These two effects produce an upward movement of the systolic blood pressure coincident with the positive pressure breath, referred to as the Δ up component of SPV. Following this Δ up, a fall in systolic pressure occurs a few beats later as the decreased venous return (preload) to the right ventricle that occurred during positive pressure inspiration is now evident as decreased preload to the left ventricle after a few cardiac cycles. The transient reduction in right ventricular volume and output leads to a smaller left ventricular stroke volume and a brief reduction in arterial pressure that occurs later in the ventilator cycle (Δ down).

An exaggerated SPV (>10 mm Hg) is observed early in the setting of hypovolemia.

An exaggerated SPV (>10 mm Hg) has been noted early in the setting of hypovolemia. This is due to a greater Δ down component. Several studies have reported that an increase in the SPV occurs prior to a fall in arterial pressure and may be a better predictor of hypovolemia than a low pulmonary capillary wedge pressure (PCWP) (<10 mm Hg). An increase in the SPV due to a greater Δ down component can also occur due to high airway pressures causing decreased venous return.

Recently, pulse pressure variation (PPV) has also been found to be a sensitive indicator of preload and, more importantly, fluid responsiveness. PPV is defined as the maximal pulse pressure (systolic minus diastolic blood pressure) less the minimum pulse pressure divided by the average of these two pressures.

The use of systolic pressure variation and pulse pressure variation is limited to those patients on mechanical ventilation. These measurements should occur when there is no spontaneous breathing. In the presence of a consistent delivered tidal volume, systolic pressure variation can be used to track the adequacy of intravascular volume over time (◘ Fig. 34.3).

The use of bedside ultrasound by pediatric intensivists to assist in the assessment of fluid status and cardiac function is becoming readily available as more training programs are incorporating this skill into the curriculum. Incorporating echocardiography into the hemodynamic assessment of patients with fluid-refractory shock may help guide further treatment decisions and changes in ongoing therapies.

34.6.4 Elimination of Pathogen

Early identification of a possible offending pathogen and aggressive source control represent a crucial component of septic shock therapy. Prompt initiation of appropriate antimicrobial therapy against the causative pathogen has been found to be one of the most important predictors of outcome. In a study from the 1980s of over 1100 adults, providing appropriate antimicrobial coverage at least 1 day prior to identification of the organism was associated with improved survival. Additionally, the pathogen itself has prognostic signifi-

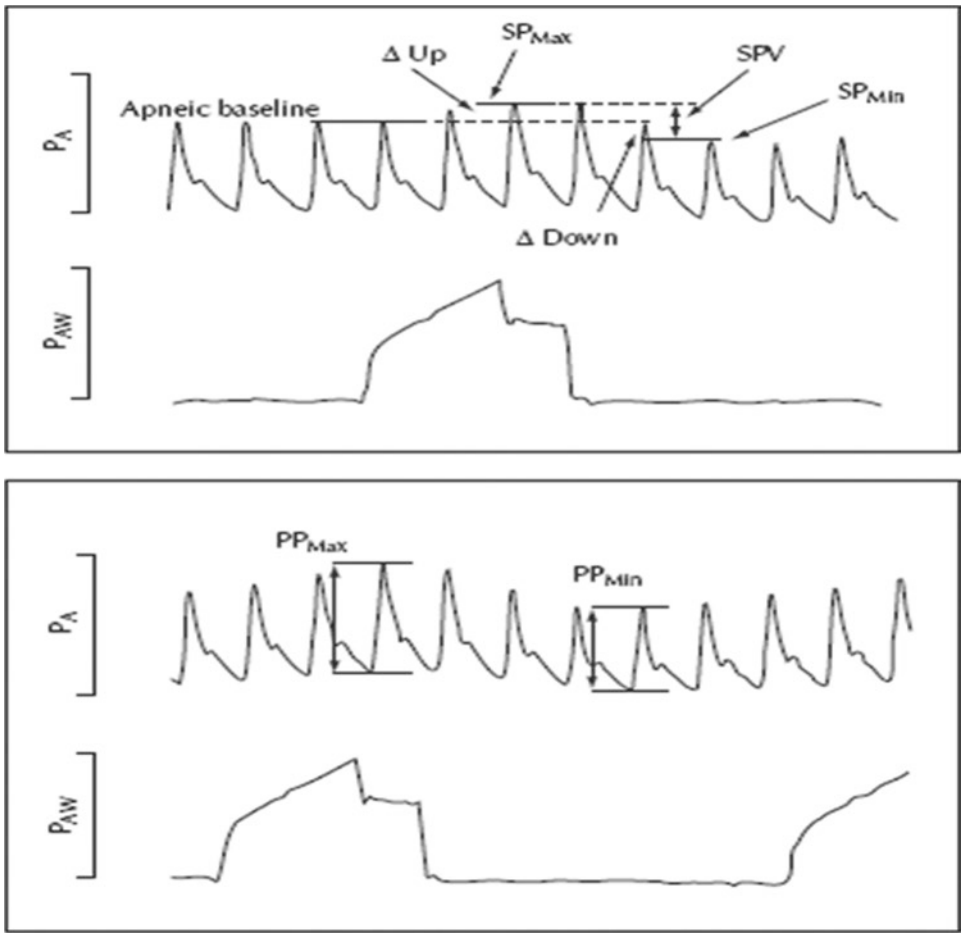

Fig. 34.3 Systolic pressure variation (SPV) and pulse pressure variation (PPV) can accurately predict which patients will be responsive to further fluid resuscitation (Gunn and Pinsky 2001). SP_{Max} maximum systolic pressure, SP_{Min} minimum systolic pressure, PP_{Max} pulse pressure maximum, PP_{Min} pulse pressure minimum, P_A arterial pressure, P_{AW} airway pressure

cance. Fungal infections, while accounting for only a minority of sepsis cases, carry the lowest survival rate, followed by gram-positive and gram-negative bacteria. Survival rate has been reported to be the highest in patients in whom no pathogen was identified.

Because of the importance of appropriate antimicrobial therapy, the decision of which agents to empirically start must balance potential side effects versus maximizing coverage. In this respect, it is important to be familiar not only with the most common causative pathogens but also the local ICU nosocomial risks and pathogen resistance patterns. Initially, broad antibiotic coverage is initiated. Neonates are most frequently placed on ampicillin and an aminoglycoside (e.g., gentamicin) or a third-generation cephalosporin such as cefotaxime. In infants and children over the age of 4–6 weeks, the decision to start vancomycin empirically should be considered in light of the antibiotic resistance of *Streptococcus pneumoniae* and the incidence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA). In addition, a third- or fourth-generation cephalosporin (e.g., ceftriaxone) should be used. Suspicion of a gram-negative infection or nosocomial infection requires additional coverage, usually in the form of an aminoglycoside, for the possibility of *Pseudomonas* species and other resistant gram-negative organisms. Because of its broad coverage, including many anaerobic species, and low renal toxicity, piperacillin/tazobactam is empirically administered with increasing frequency. The antiviral agent, acyclovir, should be administered if there is suspicion of a herpesvirus infection. In immunocompetent children, the decision to start empiric antifun-

gal therapy remains controversial. In the child who is not improving over the initial days of empiric coverage or in whom there is a higher risk for fungal infection (e.g., presence of indwelling devices, immunosuppression, or other significant comorbidities), antifungal coverage may be indicated. The development of agents equally as effective as amphotericin, but with substantially reduced nephrotoxicity such as fluconazole and caspofungin, may ultimately sway the risk/benefit analysis toward more aggressive, earlier initiation of empiric antifungal coverage in select, high-risk populations. The ability to narrow the spectrum of treatment once the causative organism has been identified will reduce the number of potential side effects and curtail the development of pathogen resistance related to imprudent use of broad-spectrum antibiotics.

34.6.5 Maintenance of Oxygen Delivery

The current mainstay of supportive care in sepsis remains the maintenance of adequate oxygen delivery in the face of myocardial depression, capillary leak, acidosis, and massive cytokine release. While some early adult studies have suggested improved outcomes when achieving supranormal levels of oxygen delivery, this approach in pediatric sepsis remains unproven. This is likely due to the fact that septic patients may have a perturbed ability to extract oxygen in addition to suboptimal oxygen delivery. Clinically, this impairment in cellular oxygen uptake may be reflected by an inappropriately high central venous oxygen saturation ($S_{cv}O_2$) in the face of a progressive and therapy-refractory acidosis. Optimizing appropriate oxygen delivery remains a clinical goal and incorporates the need for maximizing oxygen-carrying capacity. Perhaps the best assessments are determinations that provide indirect evidence of the balance between oxygen delivery and consumption such as lactate levels and mixed venous oxygen saturation.

Finally, the nutritional status of the septic child must be addressed. Patients with sepsis often have poor nutrition prior to admission to the ICU and often may not be fed in the first few days of illness. This state combined with the increased metabolic rate associated with sepsis places the septic patient at risk for protein calorie malnutrition. Intestinal hypoperfusion in combination with the absence of local enterocyte nutrition can cause mucosal barrier dysfunction and may contribute to translocation of bacteria and endotoxin from the intestine into the bloodstream. While the use of enteral feeding in critical illness has been found to improve survival and decrease hospital stay, its use must be balanced with the risk of stressing intestinal function in the face of poor splanchnic perfusion, especially in the child requiring the use of vasopressors such as epinephrine and norepinephrine. Delay in providing nutrition via enteral feeds may be preferred over early parenteral nutrition within the first week of illness. Regardless of which mode of nutrition is chosen, the goal of achieving nitrogen balance is important for allowing recovery and return to physiologic homeostasis. In the absence of enteral feedings, protection from stress-related gastrointestinal ulcer formation is advised.

34.6.6 Additional Therapeutic Modalities

Because poor outcome in sepsis has been attributed to a dysregulated proinflammatory state, anti-inflammatory agents, such as corticosteroids, have long been proposed as a potential therapeutic strategy. Anecdotally, it has been observed that some patients treated with antibiotics appear to acutely worsen

in a time frame consistent with the onset of antibiotic activity. This observation has been attributed to massive release of bacterial products following the lysis of high numbers of bacteria. To this end, investigators have demonstrated that animals treated with anti-inflammatory medications prior to receiving antibiotics experience a less severe response to bacterial lysis. Despite encouraging preclinical studies, two subsequent large adult trials using high-dose steroids early in sepsis found no improvement in mortality. Studies using lower doses of steroids over a longer period of time have suggested a possible benefit including a reduced time to cessation of vasopressor therapy. Subsequent studies based on risk stratification of pediatric patients with sepsis suggest that steroids in some endotypes of sepsis, including those with low levels of corticosteroid receptors, may increase the risk of mortality. The use of steroids may be considered in some refractory patients.

Because the host response to sepsis is mediated by circulating inflammatory molecules, it has been hypothesized that extracorporeal removal of these mediators via hemofiltration or exchange transfusion may affect outcome. Case reports suggest that arterial oxygenation and hemodynamics can be improved with the use of hemofiltration during sepsis and multiple organ failure. However, there exist many mitigating factors in evaluating the pediatric experience, and the efficacy of hemofiltration remains unproven. Challenges with instituting extracorporeal hemofiltration include difficulty with vascular access in smaller children, potential fluid and electrolyte imbalance, hypothermia, anticoagulation requirements, and acutely compromised hemodynamics during initiation. In addition, it is not known whether beneficial proteins such as albumin, immunoglobulins, clotting factors, and counter-regulatory cytokines are removed during this process. While experience suggests that hemofiltration can be safely performed in children with sepsis, it remains unclear if it will improve outcome.

Part of the inflammatory response involves cytokines that cause widespread activation of the coagulation cascade with suppression of fibrinolysis as reviewed above. Unfortunately, many of the immunomodulatory agents tried to date (anti-IL-1, anti-bradykinin, anti-endotoxin, anti-TNF-α, soluble TNF receptor, and antiplatelet-activating factor) have not shown any benefit in large, randomized clinical trials. It is hoped that improvements in study design which include thoughtful stratification of patients, timely identification of the presence or absence of a pathogen, and consideration of genetic factors that influence outcome will eventually assist in discovering and targeting pharmacologic agents that ultimately improve the outcome of the pediatric patient with septic shock.

34.6.7 Institutional Level Care Bundles

A major addition to the 2014 ACCM Practice Parameters was the recommendation for an institutional approach to sepsis through the use of care bundles. The 2020 guidelines re-affirm the value of such an institutional approach. Each institution should develop and implement four bundles: (1) a recognition bundle, (2) a resuscitation bundle, (3) a stabilization bundle, and (4) a performance bundle. The recognition bundle should contain a trigger tool that identifies alterations in vital signs and physical exam findings in at-risk populations. The trigger tool would prompt a rapid clinical assessment within 15 min and subsequent resuscitation bundle for patient meeting criteria for suspected septic shock. The resuscitation bundle should be directed to establish intravenous access within 5 min, appropriate fluid resuscitation within 30 min, broad-spectrum antibiotics within 60 min, and the appropriate use of inotropes

within 60 min. The stabilization bundle should focus on the monitoring of the therapies for appropriate resuscitation and source control of the infectious source. The performance bundle is used to assess the three prior bundles for adherence to the bundle, achievement of goals for the individual components, and assessment of barriers/unintended consequences of the implementation of the bundles as well as their sustainability. Revisions of each bundle should be based on results of the findings in the performance bundle.

In assessing the impact of bundles, Evans demonstrated the need for institutions to not only develop the bundles, but to ensure their timely execution. In that report of the New York state mandate to institute sepsis bundles, septic patients who received antibiotics and fluid boluses within 1 h (25% of the 1179 patients) as described in the bundle had a lower risk-adjusted in-hospital mortality than those patients who had the bundle completed in over 1 h.

34.7 Summary

Sepsis remains one of the most pressing clinical challenges for the pediatric intensivist. It is apparent that while a great deal is now understood about the biological and molecular mechanisms involved in sepsis, this knowledge has not yet had a dramatic impact on improving outcome. At present, therapeutic modalities for sepsis remain largely supportive and founded on the fundamental physiologic principle of providing adequate oxygen delivery and the timely institution of antimicrobial therapy. With this approach, mortality in pediatric sepsis has improved modestly over the past decades. However, the fact that over 4000 children per year continue to die in association with severe sepsis argues that further advances are needed. Realization of the goal of improving survival requires investigators committed to achieving further mechanistic insights into the physiologic, molecular, and genetic biology of sepsis, in concert with large pediatric-specific interventional trials based on those mechanistic insights.

Review Questions

1. *In comparison to adults, children are more likely to present with which one of the following hemodynamic profiles?*
   A. High cardiac index with high systemic vascular resistance
   B. High cardiac index with low systemic vascular resistance
   C. Low cardiac index with high systemic vascular resistance
   D. Low cardiac index with low systemic vascular resistance
   E. Normal cardiac index with low systemic vascular resistance

2. *Activation of the innate immune system in gram-positive bacterial sepsis is mediated by:*
   A. Toll-like receptor 2 (TLR2)
   B. TLR3
   C. TLR4
   D. TLR5
   E. TLR6

3. *Which of the following biologic effects is most accurately attributed to TNF-α?*
   A. Induction of nitric oxide synthase (iNOS)
   B. Inhibition of adhesion molecules and chemokines that facilitate leukocyte-endothelial cell adhesion
   C. Inhibition of IL-1β
   D. Inhibition of tissue factor
   E. Upregulation of protein C

4. *Which of the following statements regarding IL-1β is true?*
   A. IL-1β decreases tissue factor expression.
   B. IL-1β increases adhesion molecule expression.
   C. IL-1β inhibits monocyte activation and phagocytosis.
   D. IL-1β is the only agonist among the IL-1 family of proteins.
   E. IL-1β stimulates thrombomodulin secretion.

5. *Which of the following biologic mediators is an anti-inflammatory cytokine?*
   A. IL-1β
   B. IL-6
   C. IL-8
   D. IL-10
   E. TNF-α

6. *Which of the following cytokines functions primarily as a chemokine?*
   A. IL-1β
   B. IL-6
   C. IL-8
   D. IL-10
   E. TNF-α

7. *Which of the following statements best summarizes the biologic effects of protein C?*
   A. Antithrombotic and anti-inflammatory
   B. Antithrombotic and proinflammatory
   C. Antithrombotic but without any effect on the inflammatory process
   D. Prothrombotic and anti-inflammatory
   E. Prothrombotic and proinflammatory

8. *Once stable oxygenation and ventilation are assured, which of the following is the most important priority in the patient with septic shock?*
   A. Adequate sedation and paralysis
   B. Fluid resuscitation with 20 mL/kg of isotonic fluid
   C. Initiation of inotropic support
   D. Placement of an arterial catheter
   E. Placement of central venous access

9. *A 12-year-old male with acute lymphocytic leukemia is admitted to the pediatric intensive care unit with vancomycin-resistant Enterococcus bacteremia. His vital signs reveal a temperature of 39.6 °C, a heart rate of 145 bpm, a respiratory rate of 20 bpm, and a blood pressure of 108/35 mm Hg. He is lethargic but arousable. His pulses are bounding and his capillary refill is brisk. An arterial blood gas reveals a pH 7.31, a $PaCO_2$ 33 mm Hg, a PaO_2 65 mm Hg, an oxygen saturation of 93%, and a base deficit of (−10). The oxygen saturation of venous blood sampled from the superior vena cava is 88%. Which of the following statements best describes his clinical condition?*
   A. The young man has a primary metabolic acidosis but has a normal oxygen extraction as oxygen saturation in the superior vena cava is normally higher than elsewhere in the body.
   B. The young man has a primary metabolic acidosis, but is not in shock, evidenced by his high superior vena cava saturation.
   C. The young man has a primary respiratory alkalosis that would benefit from supplemental oxygen therapy.

D. The young man is bacteremic, but not in shock as evidenced by his bounding pulses, brisk refill, and normal systolic blood pressure.
E. The young man is in shock with inadequate oxygen extraction at the tissue level evidenced by the elevated superior vena cava saturation.

10. *It has become clear that dysregulation of the coagulation cascade occurs in sepsis as reflected by activation of procoagulant pathways, consumption of clotting factors, alterations in fibrinolysis, and reduced anticoagulant activity. Which of the following components of coagulation is increased during sepsis?*
A. Antithrombin III (AT-III)
B. Plasminogen activator inhibitor type I (PAI-1)
C. Protein C
D. Protein S
E. Tissue factor pathway inhibitor (TFPI)

Answers

1. C
2. A
3. A
4. B
5. D
6. C
7. A
8. B
9. E
10. B

Suggested Readings

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Overwhelming Infections in Pediatric Critical Care

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Contents

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Learning Objectives

- To describe key strategies used to identify the source of infection during sepsis.
- To describe clinical features, the pathogenesis, and treatment of toxic shock syndrome.
- To identify diagnostic features of infectious endocarditis and Lemierre syndrome.
- To recognize the classic clinical findings that should raise suspicion for necrotizing fasciitis and to describe the appropriate diagnostic and therapeutic interventions for this condition.
- To describe the pathogenesis, most common pathogens, and empiric antimicrobial therapy for acute bacterial meningitis.
- To understand the approach toward the management of brain abscesses and the indication for surgical intervention.
- To review the various common viral pathogens that can cause encephalitis and myelitis.
- To delineate the approach to viral and bacterial pneumonia in a critically ill child.
- To describe the approach toward diagnosing and treating overwhelming infections in immunocompromised hosts such as patients with malignancies and transplantation.
- To highlight the most common overwhelming infections in children due to travel-related exposure.
- To recognize the potential pathogens and typical empiric antimicrobial regimens for key infectious processes.

35

35.1 Introduction

The evaluation of a critically ill child with an infection requires a systematic approach and careful attention to detail. Specific history and physical exam elements may provide key information regarding possible infectious exposures, determine host susceptibility, and define the infectious process and body site. Such information is pivotal to the initiation of appropriate antimicrobial therapy and lifesaving interventions in a timely and thoughtful manner. Timely diagnostic and therapeutic decisions may need to be made at times without the guidance of an infectious diseases specialist. This chapter aims to provide an approach to a variety of life-threatening infections in children. For each infectious process, the pathogenesis, potential organisms, and treatment nuances will be described. In the simplest of terms, an infection occurs when a pathogen overcomes the host defense. Therefore, in addition to identifying the pathogen, it is comparably important to understand the susceptibility of the host to that infection.

35.2 Bloodstream Infections

In order to most effectively initiate and manage the treatment of infections, it is important to identify the underlying insult and to understand its pathophysiology. Bacteremia from an undefined source is often the initial situation in the critical care environment. Blood cultures, with appropriate weight-based blood volume (2–6 mLs), are the gold standard for the detection of bacteremia, but sample acquisition should not delay antimicrobial initiation. When bacteremia is present in the setting of a focal infectious disease state, there is an increased

severity of the illness often resulting in an increased length of hospitalization, a higher likelihood of shock, and multiorgan dysfunction. Thus, in undifferentiated sepsis, a thorough exam along with targeted laboratory and imaging studies is necessary to evaluate for specific organ involvement such as pneumonia, meningitis, urinary tract infection, and bone/joint/soft issue infection. Patient factors including vaccination status, age, immunosuppression, retained foreign devices (e.g., catheters), and recent surgery are all important. Patient exposures including sick contacts, animal exposure, foodborne risks, and recent travel may also be helpful in identifying an infectious source. Ultimately, localized treatment of the source of infection with antimicrobials and targeted interventions are paramount to mitigate organ dysfunction. In those with central venous catheters, empiric treatment should include broad-spectrum antimicrobials against a variety of pathogens including *Staphylococcus aureus*. It is important to note that prolonged bacteremia increases the risk of endocarditis, osteomyelitis, and abscess formation.

In addition to bacteremia, fungal bloodstream infections should also be considered in the pediatric intensive care unit (PICU) setting given their high mortality (16–18%). Patients at increased risk for fungemia include those with central venous catheter access (up to 50% of fungemia cases occur in patients with central lines), prolonged antibiotic exposure, parenteral nutrition use, immunosuppressed status, or underlying oncologic, gastrointestinal, cardiac, or genitourinary diagnosis/pathology (▶ Box 35.1). *Candida* species are the most common causes of fungal bloodstream infections with each species having its own unique antimicrobial sensitivities. *Candida* species can typically be detected in modern standard blood culture systems. However, if there is high clinical concern, particularly for a non-*Candida* fungus such as *Fusarium* species, a specific fungal blood culture should be obtained. Although angioinvasive, *Aspergillus* cannot typically be isolated via blood culture in contrast to *Fusarium*. Antifungal therapy should be initiated accordingly (i.e., echinocandin for *Candida* and amphotericin B for molds) and in a timely manner.

Box 35.1 Risk Factors for Fungal Bloodstream Infections

- Central venous catheter
- Prolonged antibiotic use (over 7 days)
- Parenteral nutrition use (TPN, PPN)
- Immunosuppressed status
  - Transplant recipient
  - Innate/hereditary immunodeficiency
  - Acquired immunodeficiency including HIV and medication-induced immunosuppression
- Certain disease states
  - Cancer
  - Atypical anatomy or foreign object presence in the gastrointestinal, cardiac, or genitourinary system

TPN total parenteral nutrition, *PPN* peripheral parenteral nutrition, *HIV* human immunodeficiency virus

Sepsis from overwhelming viral infection with viremia can occur with a variety of viruses in the pediatric population. Viremia, defined by qualitative virus detection in the blood or by quantitative viral blood loads (different for each virus) using molecular techniques, is not routinely performed as part of the initial

assessment of most children with sepsis in the PICU. Although viremia can trigger sepsis physiology, especially in the setting of high viral replication states (e.g., human immunodeficiency virus (HIV), hepatitis, cytomegalovirus (CMV), Epstein-Barr virus (EBV), adenovirus), the value of detection or monitoring with viral polymerase chain reaction (PCR) is still unclear outside the immunocompromised patient populations.

Bloodstream infection:

- The daily evaluation of the necessity for invasive tubes and catheters and the use of care bundles for the placement and maintenance of central venous lines and urinary catheters reduce invasive infections.

The prevention of bloodstream infections is another important concept with importance specifically applied to the regular evaluation of the need for each invasive catheter, their timely discontinuation/removal, and the use of insertion and maintenance care bundles. The use of the United States Centers for Disease Control and Prevention (CDC) recommendations has been found to decrease central venous catheter-associated bloodstream infection (CLABSI) and catheter-associated urinary tract infection (CAUTI) rates by more than 40% in the PICU (▶ Chap. 37).

35.2.1 Toxic Shock Syndrome

Toxic shock syndrome occurs as a significant host response to a bacterial exotoxin-mediated process with a classic presentation of fever, scarlatiniform or erythroderma rash with possible skin desquamation, strawberry tongue, and a shock state with multiorgan dysfunction. Common causative organisms are *Staphylococcus aureus* and *Streptococcus pyogenes*. Patients may present with a body-site-specific infection (e.g., cellulitis, deep soft tissue, etc.) but may also have "toxemia" that occurs with toxin production from a colonizing strain of *Staphylococcus aureus* or *Streptococcus pyogenes* on a mucosal surface without an obvious tissue source of infection. Classically, toxic shock syndrome has been associated with certain types of tampon use in the past – although not zero, this risk is much lower with the use of modern, current-day brands of tampons. Adolescents may continue to be at increased risk related to retained tampon use and experimental non-sterile foreign object insertion into body cavities. In addition, post-varicella bacterial skin and soft tissue infections, influenza-associated bacterial pneumonia, blunt trauma, necrotizing fasciitis, and nonsteroidal anti-inflammatory drug (NSAID) use have all been associated with an increased risk of toxic shock syndrome.

Toxic shock syndrome occurs when bacterial exotoxins act as superantigens, effectively bypassing typical or expected antigen-mediated immune responses by the human host. Bacterial antigens such as PVL and fnbA in *Staphylococcus aureus* and SPEA, SPEB, and SPEC in *Streptococcus pyogenes* can stimulate a robust host immune response producing a rapid onset of clinical shock. Patients have a rapidly progressive illness and, due to the toxin-mediated process, often have negative blood cultures or late positivity due to low-density bacteremia. Once the clinical course of shock is able to be mitigated with aggressive fluid management, cardiovascular and respiratory support, removal of the offending agent, and the appropriate antibiotics with source control, patients tend to improve more rapidly than would occur in septic shock presentations from other etiologies. Empiric antimicrobial regimens should target *Staphylococcus aureus* and *Streptococcus pyogenes*, combining the bactericidal coverage of vancomycin with a beta-lactam drug such as nafcillin or cefazolin and including a protein synthesis-inhibiting antibiotic such as clindamycin (linezolid has also been used but less well established). Clindamycin is of benefit as it has the ability to target bacterial ribosomes which are essential for exotoxin production. The use of intravenous immune globin (IVIG) with TSST-1 antibody presence has been proposed in those patients with poor response to antibiotics and initial supportive management.

However, results of studies assessing empiric IVIG use in toxic shock syndrome have demonstrated mixed results and uncertain benefit. In general, IVIG should be used with caution and not routinely in toxic shock. A variety of other serious conditions can sometimes mimic toxic shock syndrome and should be considered in the differential diagnosis including rickettsial infections (e.g., Rocky Mountain spotted fever), meningococcemia, Kawasaki disease, Stevens-Johnson syndrome, and severe vial sepsis syndromes.

35.2.2 Endocarditis

Endocarditis is of particular concern in children with prolonged bloodstream infection, those with congenital heart disease pre- and/or post-repair/operation and central venous catheters, and adolescents with exposure to intravenous drug use (▶ Box 35.2). Classic immunologic (i.e., Osler nodes, Roth spots) and vascular (petechiae, emboli, Janeway lesions, splinter hemorrhages) signs are uncommon at the time of presentation in children, although they are still included in clinical diagnosis calculators such as the Modified Duke Criteria (▶ Box 35.3). Other clues of endocarditis on clinical exam include declining systemic oxygen saturation in cyanotic congenital heart disease, new heart block, asthma-like or pulmonary embolism symptoms, and fever in the setting of malaise and heart failure. Repetitive blood cultures and echocardiogram are routine components of evaluation. The initial antibiotic therapy should provide broad antimicrobial activity (ideally bactericidal) against *Staphylococcus aureus*, *Streptococcus* species including viridans group streptococci, coagulase-negative staphylococci, enterococci, and Gram-negative bacilli often requiring a multidrug regimen. Additionally, less common organisms should be considered in culture-negative endocarditis, including the HACEK (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species) organisms of the oropharynx, as well as *Bartonella*, *Brucella*, *Mycoplasma*, *Legionella*, and *Coxiella burnetii*. In high-risk patient populations where fungal etiologies are possible, the addition of amphotericin B, with or without 5-fluoruracil (5-FC), should be considered. Surgical indications and timing are still not clearly defined for children, but early involvement with cardiology and cardiothoracic surgery services is important in ongoing care.

Bloodstream infection:
- The HACEK organisms should be considered in culture-negative endocarditis. They consist of the following organisms:
  - *Haemophilus* species
  - *Aggregatibacter* species
  - *Cardiobacterium hominis*
  - *Eikenella corrodens*
  - *Kingella kingae*

Box 35.2 Risk Factors for Infectious Endocarditis
- Central venous catheter
- Congenital heart disease with ongoing shunt physiology or valvular dysfunction
- Recent repaired congenital heart disease
- Recent dental procedures

Box 35.3 Modified Duke Criteria
Consider infectious endocarditis if two major criteria or one major and three minor criteria or five minor criteria

Major criteria
- ≥2 blood cultures with concerning organism (viridans streptococci, HACEK, *Staphylococcus aureus*, enterococci) or persistent bacteremia separated by at least 12 h

- Echocardiogram with oscillating intracardiac mass on valve or surrounding anatomy, dehiscence of prosthetic valve, new valvular regurgitation, or abscess

Minor criteria

- Predisposing heart condition (unrepaired congenital heart disease, intravenous drug use).
- Fever (≥38.0 °C)
- Vascular phenomena (major arterial emboli, pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions)
- Immunologic phenomena (glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor)
- Other concerning positive blood cultures or serology for endocarditis

35.2.3 Endovascular Infections

In addition to endocarditis, another endovascular source of continuous bacteremia is septic thrombophlebitis. Lemierre syndrome, or septic thrombophlebitis of the internal jugular vein, is the most classic presentation. This syndrome presents as pharyngitis which progresses to septic thrombophlebitis of the internal jugular vein in 4 or 5 days, sometimes with an associated peritonsillar abscess. It occurs most commonly in healthy adolescents. The patients are often critically ill with hemodynamic instability and/or respiratory distress secondary to septic emboli to the lungs resulting in empyema and pulmonary abscess. The most common pathogen cultured is *Fusobacterium necrophorum*, a Gram-negative oral anaerobe, which produces a significant amount of lipopolysaccharide (LPS) as an endotoxin, thus accounting for some of its virulence. Although *Staphylococcus aureus* and other oral anaerobes may also cause septic thrombophlebitis of the internal jugular vein in a small portion of patients, bacteriologists classically refer to Lemierre syndrome as the disease caused by *Fusobacterium* species. Empiric therapy should include ampicillin-sulbactam, and if there is concern for resistant Gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), the addition of vancomycin should be considered.

35.3 Necrotizing Skin and Soft Tissue Infections (SSTI)

Patients with necrotizing skin and soft tissue infections (SSTI) generally present critically ill with the potential for rapid deterioration and the loss of limb or life. Patients with necrotizing fasciitis generally have involvement of the superficial fascia that tracks rapidly along the subcutaneous tissue to the muscle. The initial introduction of the pathogen occurs with contamination of a breakage in the skin such as a minor wound, a puncture, or an abrasion. The virulent organisms then rapidly divide spreading across the superficial fascial planes causing extensive tissue necrosis.

Necrotizing fasciitis:

- The classic presentation for necrotizing fasciitis includes pain disproportionate to the skin findings, "wooden" induration, and systemic signs of severe illness.

These patients can present with signs of cellulitis with erythema and induration or may have a paucity of skin findings. Pain out-of-proportion to the cutaneous erythema with a "wooden" hard induration on palpation is a classic presentation of necrotizing fasciitis. There may be crepitus with palpation, consistent with the presence of subcutaneous gas; there may also be bullae or

skin necrosis. Due to extensive tissue necrosis and, at times, the presence of toxin-producing pathogens such as *Streptococcus pyogenes*, patients may present with high fevers, altered mental status, hypotension, and multiorgan involvement. Infections can be monomicrobial or polymicrobial. Polymicrobial infections occur in patients with underlying chronic medical conditions such as diabetes, history of abdominal surgeries, or trauma. Monomicrobial infections can occur in otherwise healthy young children. Common pathogens include *Streptococcus pyogenes*, *Staphylococcus aureus* (either methicillin-susceptible *Staphylococcus aureus* (MSSA) or MRSA), anaerobic streptococci, *Clostridium perfringens*, as well as other *Clostridium* species. Polymicrobial infections that extended from the perineum and genital areas (i.e., Fournier gangrene) are associated with Gram-negative organisms as well as intra-abdominal anaerobes. If there is exposure of a wound to contaminated water, *Vibrio vulnificus* and *Aeromonas hydrophila* must be considered, and additional coverage may be needed (doxycycline and ceftriaxone or ceftazidime for *Vibrio vulnificus* and doxycycline and ciprofloxacin for *Aeromonas hydrophila*).

Computerized tomography (CT) or magnetic resonance imaging (MRI) may reveal ill-defined edema or the presence of gas; these findings lack sensitivity and specificity and may delay diagnosis and timely surgical intervention. The gold standard for diagnosis is the intraoperative appearance of the fascia and subcutaneous tissue. In cases of necrotizing fasciitis, subcutaneous fascia and the surrounding tissue have extensive edema and can appear dull gray in color with areas of necrosis. There may be no significant purulence or thin, scant exudates may be present. The infected tissue should be sent for bacterial aerobic and anaerobic cultures; this will aid in isolating definitive pathogens.

Emergent surgical debridement is the most important therapeutic intervention for necrotizing fasciitis; it is imperative for obtaining source control and can be lifesaving and limb-preserving. Patients may need to return to the operating room for daily debridement until the surgical team is satisfied that there is no further necrosis. Empiric antimicrobial coverage should include coverage for a potential polymicrobial infection until cultures are finalized. Empiric therapy should include the addition of anaerobic coverage to the use of a bactericidal beta-lactam (antimicrobial class that includes penicillins, cephalosporins, and carbapenems). Empiric therapy should cover *Streptococcus pyogenes*, MSSA, and anaerobes and, if there is a concern, should also cover MRSA and Gram-negative bacilli. Patients can be started on broad-spectrum antibiotics such as vancomycin or linezolid with piperacillin-tazobactam or imipenem or with ceftriaxone and metronidazole. Clindamycin can be added to these regimens for its ability to target bacterial ribosomes because ribosomes are essential for exotoxin production.

Necrotizing fasciitis:

- Surgical debridement is a necessary diagnostic and therapeutic intervention for necrotizing fasciitis.

If *Streptococcus pyogenes* infection is suspected, both intravenous penicillin and clindamycin should be used. Animal models note the "Eagle effect" with *Streptococcus pyogenes*, where there is a failure of high-dose penicillin when used alone for treatment of deep-seated infections. Generally, *Streptococcus pyogenes* is exquisitely susceptible to penicillin therapy. This noted failure is postulated to be due to a reduced bactericidal effect of high-dose penicillin when there is a large bacterial burden, and the bacteria remain in a stationary growth phase due to nutrient deficiency as they reach the end of a fascial or muscle plane. If bacteria remain in a stationary phase, then penicillin is rendered ineffective because it targets dividing bacteria by interfering with new cell wall formation. Intracellularly active ribosomal agents such as clindamycin may be more effective in this setting because they do not target a dividing cell wall. In addition to prompt surgical debridement and combination therapy of penicillin and clindamycin, IVIG is used in some instances of *Streptococcus pyogenes* necrotizing fasciitis, particularly in more severe infections to provide

neutralizing antibodies against bacteria and exotoxin. There is no definitive evidence for IVIG in this role, but there are several case reports, case series, and small case-control trials that demonstrate some benefit. However, a randomized controlled trial in Europe demonstrated no clear benefit of IVIG. Further studies are needed to make routine recommendations regarding IVIG use in severe *Streptococcus pyogenes* necrotizing fasciitis.

35.4 Central Nervous System (CNS) Infections

35.4.1 Acute Bacterial Meningitis

CNS infections:

- *Streptococcus pneumoniae*, *Haemophilus influenzae* type B (HiB), and *Neisseria meningitidis* are the most common causes of acute bacterial meningitis in infants beyond the neonatal period and children.

Children with central nervous system (CNS) infections can be critically ill on initial presentation. The incidence of acute bacterial meningitis beyond the neonatal period has declined significantly since the advent of pneumococcal and *Haemophilus influenza* type B (HiB) vaccination. The most common bacterial pathogens that cause acute bacterial meningitis in otherwise healthy children beyond the neonatal period are *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenza* type B (HiB).

The pathogenesis of acute bacterial meningitis in otherwise normal hosts consists of three phases: (1) nasopharyngeal colonization, (2) bacteremia, and (3) invasion of the blood-brain barrier (BBB). Nasopharyngeal colonization begins with new acquisition of the pathogen. Next, there is invasion from the nasopharynx into the bloodstream by the organism. The bacteria then evade the host immune response in the blood and are resistant to phagocytosis due to their polysaccharide capsule. After successfully evading clearance, the pathogen then reaches the BBB which consists of a physical barrier of endothelial cells and their tight junctions within the cerebral microvasculature. The bacteria then use their virulence factors to cross the BBB. More specifically, *Neisseria meningitidis* use pili to bind to cell surface receptors, and *Streptococcus pneumoniae* hijack host cell receptors and signaling pathways to cross the human brain endothelial cell and reach the meninges and brain, whereupon they cause cell death and necrosis.

Streptococcus agalactiae or group B *Streptococcus* (GBS), *Escherichia coli*, and *Listeria monocytogenes* are the most common causes of acute bacterial meningitis in neonates. The mucous membranes of newborns are colonized by these pathogens during labor and delivery. Invasion into the bloodstream can occur immediately (early-onset sepsis) or later (late-onset sepsis). Neonates have the same physical BBB as older infants, children, and adults; however, they lack the humoral immunity to achieve bacteremia clearance in comparison to older patients. These bacteria using their virulence factors (e.g., *Escherichia coli* and their pili) are able to cross the brain endothelial cell and reach the meninges.

Suspicion for bacterial meningitis should be raised in infants and children who have fevers, irritability, severe headaches, and neck stiffness. In later stages, patients can have signs of CNS depression such as somnolence and other changes in mental status. The physical exam may reveal a bulging fontanelle, signs of meningismus, and/or nuchal rigidity. A lumbar puncture should be performed as soon as possible to ascertain the diagnosis. The cell count, glucose and protein levels, as well as a bacterial Gram stain and culture must be sent from the cerebral spinal fluid (CSF). The analysis of aberrant values of these CSF indices can help differentiate between bacterial, viral, and mycobacterial infection (Table 35.1).

Table 35.1 Typical cerebrospinal fluid (CSF) indices in central nervous system infections

Potential pathogens	CSF leukocytes (cells/μL)	CSF glucose	CSF protein
Bacteria	WBC > 500 Neutrophilic predominance	<45 mg/dL	>100 mg/dL
Virus	WBC 5–500 Lymphocytic predominance	Normal[a]	50–100 mg/dL
Fungi	WBC 5–500 Neutrophilic predominance	<45 mg/dL	>100 mg/dL
Mycobacterium tuberculosis	WBC 5–500 Lymphocytic predominance	10–45 mg/dL	>200 mg/dL

WBC white blood cell
[a]Relative to serum glucose

Antimicrobial therapy should be started as soon as possible using meningitic dosing parameters. Typical empiric therapy for presumed bacterial meningitis in patients beyond the neonatal period is vancomycin and ceftriaxone. Ceftriaxone offers coverage against *Streptococcus pneumoniae*, *Neisseria meningitidis*, and HiB. Vancomycin is added to provide coverage for the possibility of ceftriaxone-resistant *Streptococcus pneumoniae*. Resistance rates differ by location and local susceptibility data can be found in institutional antibiograms. The concomitant use of dexamethasone along with empiric antimicrobial therapy is controversial in pediatrics. Data support the use of dexamethasone in HiB meningitis; those who receive concomitant dexamethasone along with antimicrobial therapy have been found to have significantly less hearing loss. The dexamethasone should be administered before or at the same time as the first dose of antibiotics. However, data assessing the use of dexamethasone for *Streptococcus pneumoniae* meningitis do not consistently demonstrate benefit.

There may be significant sequelae in critically ill patients with meningitis despite prompt and appropriate therapy. The most common sequelae include sensorineural hearing loss. Up to 30% of patients with pneumococcal meningitis and up to 8% of patients with meningococcal meningitis have been found to have sensorineural hearing loss. All patients should have auditory brainstem response (ABR) testing performed prior to discharge to document potential hearing loss. In addition, severe, irreversible brain dysfunction can particularly occur in patients with pneumococcal meningitis because the heavy bacterial burden can cause significant vasculitis and ischemia. In such patients, an MRI of the brain can document the extent of the damage and guide prognosis.

CNS infections:
- Sensorineural hearing loss is the most common sequelae after acute bacterial meningitis.

35.4.2 Focal Suppurative CNS Infections

In addition to hematogenous spread, bacteria can directly invade the CNS from either disruption of the BBB with trauma or surgery or from associated sinusitis or mastoiditis. In this manner, they can produce brain abscesses, subdural or epidural empyemas, and/or dural venous sinus thromboses. Children with cyanotic congenital heart disease are at increased risk for brain abscesses because bacteria can bypass the reticuloendothelial cells of the lungs with right-to-left

shunting and evade clearance. Patients with focal pyogenic CNS infections generally present with fevers, headaches, vomiting (without diarrhea as a sign of increased intracranial pressure), as well as focal neurological deficits.

The diagnosis of these infections is confirmed by brain imaging (either with MRI or CT) with intravenous contrast. *Streptococcus pneumoniae*, HiB, and *Neisseria meningitidis* can all cause subdural empyemas as pyogenic complications of acute bacterial meningitis and associated cerebritis. However, other streptococcal species, particularly those of the *Streptococcus milleri* group such as *Streptococcus anginosus*, are isolated most commonly from brain abscesses. CNS infection with these streptococci generally occurs as a direct extension from complicated sinusitis. *Staphylococcus aureus*, either MSSA or MRSA, is most commonly isolated after head trauma with skull fractures or penetrating wounds causing disruption of the BBB and introduction of skin organisms into the CNS. *Staphylococcus aureus* is also the most common pathogen isolated from spinal epidural abscesses after inoculation of the site via hematogenous septic emboli. Brain abscesses as a complication of sinusitis (generally in the frontal lobe) or mastoiditis (in the temporal lobe) tend to be polymicrobial with the simultaneous presence of nasopharyngeal anaerobes. Therefore, in addition to empiric vancomycin and ceftriaxone, intravenous metronidazole is used to treat such infections.

CNS infection:

- Empiric anaerobic coverage with intravenous metronidazole may be needed in addition to vancomycin and ceftriaxone for the treatment of brain abscesses due to direct extension from mastoiditis or sinusitis.

Patients who are clinically stable with brain abscess less than 2–3 cm in diameter, with multiple small abscesses, with an abscess in a critical area of the brain that cannot be approached safely with surgery, or with a known pathogen isolated from either CSF, blood, sinus, or middle ear cultures, may qualify for medical therapy alone. In these select group of patients, careful monitoring and serial imaging may be necessary to document resolution of the abscess using antimicrobial therapy alone (i.e., no surgical intervention). Otherwise, a surgical approach, either by stereotactic drainage or excisional evacuation, is necessary. The use of adjunctive steroids is controversial in the treatment of a brain abscess and is generally not recommended. However, a short course of intravenous dexamethasone may be necessary if there is life-threatening CNS edema causing increased intracranial pressure, impending herniation, and/or neurological deterioration. The duration of antimicrobial therapy is generally a protracted course; it can be 6–8 weeks if there is associated osteomyelitis (i.e., involvement of the frontal bone in Pott puffy tumor) or as short as 4 weeks if there is no presence of osteomyelitis. However, antimicrobial therapy is generally continued until complete resolution of the abscess is documented on repeat imaging.

35.4.3 Ventricular Shunt Infections

Ventricular shunts are a common treatment for hydrocephalus. The majority of ventricular shunt infections occur within the first month after surgery, with almost all of them occurring within the first 6 months to a year after placement or revision. With the development of care bundles reflecting best practices in the strictly sterile placement of ventricular shunts, the rate of shunt infections has declined in many institutions. However, these infections still account for a significant proportion of hospital-wide surgical site infections and remain a significant cause of morbidity. These infections are believed to occur by intraoperative introduction of pathogens as the CNS is being traversed for the shunt placement. Within the shunt, these pathogens then form a biofilm. Biofilm is a complex formation of microorganisms and the extracellular protein matrix that they endogenously produce, creating a thick, impenetrable layer on a device surface. The presence of this biofilm does not allow appropriate concen-

trations of antimicrobial therapy to penetrate the site of infection. Thus, the eradication of such infections becomes nearly impossible without removal of the shunt.

Depending on the pathogen and the organism burden, patients with ventricular shunt infections will have a range of clinical presentations with varying degrees of acuity. These patients may present with fevers, headaches, signs of shunt malfunction, and wound dehiscence. CSF sampling from the shunt is necessary to confirm the diagnosis. The most common pathogen causing ventricular shunt infection is coagulase-negative staphylococci (CoNS) such as *Staphylococcus epidermidis*. Other common pathogens include *Staphylococcus aureus*, *Propionibacterium acnes*, and Gram-negative organisms such as *Pseudomonas* species. Therefore, empiric antimicrobial coverage for shunt infections is generally vancomycin (for CoNS coverage) and cefepime (for pseudomonal coverage) at meningitic dosages. Of note, there is no definitive efficacy and safety data for the intraventricular administration of antimicrobial therapy in pediatrics. Thus, the intraventricular administration of antibiotics should not be routinely used to treat ventricular shunt infections without the expert guidance from a pediatric infectious diseases specialist. Shunt removal is an essential part of management, and due to the underlying hydrocephalus, a temporary external ventricular drain (EVD) is then placed. As a result, these patients are generally managed in the PICU. Repeat CSF sampling from the EVD is necessary to document bacterial clearance so that appropriate timing for replacement of the shunt can occur.

35.4.4 Encephalitis

CNS infection:

- The classic triad for presentation of infectious encephalitis is fever, headache, and altered mental status.

Infectious encephalitis presents with the classic triad of fever, headache, and altered mental status. The most common pathogen that causes aseptic meningitis and encephalitis in the United States is enterovirus. Typically, this viral infection has a benign course and is self-limiting; most infected children will not need pediatric critical care services. However, with the rise in cases of acute flaccid myelitis in North America in 2014 and its association with enterovirus D68 (EV-D68), there has been renewed interest in the neurotropic nature of this virus. Along with severe respiratory illness in asthmatics, EV-D68 has been implicated in patients with acute paralysis of a limb and/or cranial nerve abnormalities. MRI findings in these patients reveal gray matter involvement in regions of the brain and spinal cord as well as in nerve roots. Suspect cases should be referred to, and discussed with, the CDC for further guidance. Treatment is largely supportive. Many institutions use IVIG for boosting humoral immunity, but there are no conclusive data demonstrating efficacy.

Other viruses that cause encephalitis include herpes simplex virus type I and type II (HSV-1, HSV-2) and varicella zoster virus (VZV). Young children with HSV encephalitis generally present with fevers, altered mental status, and seizures. The temporal lobe is classically involved. Varicella zoster is known to cause CNS vasculitis leading to cerebral ischemia. Both viruses are capable of producing severe necrotizing encephalitis. If HSV or VZV encephalitis is suspected, then empiric intravenous acyclovir must be started, and CSF must be obtained for PCR testing for these viruses. HSV cannot be cultured from the CNS, and therefore, PCR testing is the gold standard. Primers for the PCR testing differ from institution to institution with varying sensitivities (75–100%). A negative test for HSV in a patient with high pretest probability must be interpreted with caution if the PCR test has poor sensitivity.

Several other viruses such as arboviruses including West Nile Virus, eastern equine virus, and St. Louis encephalitis virus can present with severe CNS dysfunction. The incidence of these infections peaks in the summer and high suspicion with relevant epidemiological data is required to make the diagnosis. The diagnosis is confirmed by positive antibody testing in the CSF and acute and convalescent serum samples. RNA PCR testing is available for West Nile Virus and positive testing is specific for the infection. The treatment is supportive.

35.5 Pneumonia/Pulmonary Infections

Pneumonia and acute pulmonary infections are described in detail in ▶ Chap. 33. Although not common, life-threatening complications may occur with both viral and bacterial pneumonia. Obviously, respiratory failure and/or ARDS may occur and are associated with both mortality and morbidity. Complications of pneumonia often result in prolonged hospitalization, new morbidities, and increased cost and care needs during and after hospitalization. In addition, other, non-respiratory and potentially life-threatening conditions may be associated with pneumonia including severe electrolyte abnormalities from the syndrome of inappropriate antidiuretic hormone (SIADH) secretion, hematologic disturbances such as the hemolytic uremic syndrome (HUS) and disseminated intravascular coagulopathy (DIC), and sepsis with multiorgan dysfunction. Pneumonia results in severe sepsis and/or a shock state in less than 5% of all pediatric cases. However, rates of bacteremia and empyema are higher with complicated pneumonia from *Staphylococcus aureus* and *Streptococcus pneumoniae* compared with other bacterial etiologies. Urgent evaluation and drainage of empyema or large pleural effusions to achieve source control should be considered in critically ill children with worsening respiratory and/or cardiovascular status. Percutaneous chest tube placement with the instillation of fibrinolytic therapy and/or surgical intervention (i.e., video-assisted thoracoscopic surgery (VATS)) are often necessary, although the exact timing and order of these intervention(s) remain variable with studies supporting different approaches. Pleural fluid cultures should be sent although the yield is often below 30% due to antibiotic initiation prior to sampling.

Complications of bacterial lower respiratory tract infections can include necrotizing pneumonia with subsequent lung entrapment and/or bronchopulmonary fistula formation, often diagnosed by a persistent chest tube air leak. Although bronchopulmonary fistula formation is an uncommon complication, it is associated with increased mortality. In the setting of a bronchopulmonary fistula, fibrinolytic therapy may hinder pleural/lung parenchymal healing and may indicate a need for decortication by thoracotomy or partial pneumonectomy.

In the absence of expected clinical improvement with antibiotic regimens for usual bacterial pneumonia pathogens in the first 48–72 h of empiric treatment, additional evaluation for the causative agent should be considered. Other bacterial pathogens such as *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella*, and *Fusobacterium necrophorum* should be considered, and antimicrobial regimens expanded as indicated.

Viral pneumonias present more commonly as bilateral and/or multi-lobar disease than bacterial infections. They also differ from typical bacterial pneumonias in that they tend to present with less sepsis-like symptoms and with more diffuse, respiratory clinical findings. Life-threatening illness can occur, however, and the child with viral pneumonia may require additional therapies

such as steroids and/or antiviral regimens. Viral lower respiratory tract infections that are more likely to require critical care services are adenovirus, influenza, respiratory syncytial virus (RSV), measles, and CMV, along with less common etiologies such as hantavirus and travel-related viral exposures. Additionally, higher complication rates have been associated with certain infections such as influenza A. Although antiviral therapy has been utilized in the setting of influenza (oseltamivir, peramivir, baloxavir) and vitamin A in measles treatment in non-USA settings, there are limited data regarding the use of antiviral therapy in other viral pneumonia states including RSV.

35.6 Special Populations

In approaching a patient with a life-threatening infection, consideration of the host susceptibility is imperative. In addition to the most common virulent pathogens described above, immunocompromised patients may have overwhelming infections with opportunistic pathogens. When treating an infection in a child with primary immunodeficiency, it is important to understand the specific portion of the immune system that is affected and whether it is due to a paucity of immune cells and/or impairment in function. The type of immune defect may render the patient vulnerable to certain pathogens. For example, patients with abnormalities in phagocytosis are at high risk for deep-seated infections with catalase-positive organisms such as *Staphylococcus aureus* and *Burkholderia* species (◘ Table 35.2).

Patients with neutropenia due to chemotherapy and transplant recipients may have varying degrees of immunosuppression depending on the type and timing of the immunosuppressive agents they have received. It is important to have a comprehensive understanding of these factors when these children present with an infection. Obtaining an extensive exposure history may also be valuable in caring for these patients. Along with reviewing their travel history, any exposures to contaminated food and water or sick contacts should be solicited. Additionally, understanding the donor and recipient status of certain viruses, particularly the herpesvirus family, is essential in caring for hematopoietic cell and solid organ transplant recipients.

35.6.1 Sepsis in Oncological Patients with Neutropenia

Fever in an oncology patient with neutropenia represents a medical emergency and these patients will need prompt evaluation and treatment. These patients generally have high risk of invasive infections due to a low number of functioning granulocytes, loss of mucosal integrity with mucositis leading to translocation of bacteria, and the presence of central venous catheters.

Upon presentation, blood cultures from each catheter lumen should be obtained, and concomitant peripheral blood cultures can be obtained to increase the yield. Immediate administration of antipseudomonal therapy is recommended and is often a fourth-generation cephalosporin such as cefepime, while piperacillin-tazobactam and carbapenems can be considered for alternative therapy. Generally, febrile neutropenic patients with hemodynamic instability will be monitored in the PICU; in such patients, the addition of vancomycin and an aminoglycoside (gentamicin or tobramycin) to the cefepime is recommended. The addition of vancomycin and an aminoglycoside should also be considered if there is a history of colonization with resistant organisms in the patient or high institutional rates of resistance. If there is concern for an intra-abdominal source

Special population:
- Oncology patients with fever and neutropenia need empiric antimicrobial therapy with antipseudomonal coverage.

Table 35.2 Primary immunodeficiencies and risk of infection

Common immune defects	Common associated conditions	Clinical features	Potential pathogens
Neutrophil defects	Chronic granulomatous disease Leukocyte adhesion deficiency Chédiak-Higashi syndrome	Recurrent skin and deep-seated abscesses (e.g., lung abscesses)	Bacterial pathogens *Staphylococcus aureus* (MSSA, MRSA) *Burkholderia* spp. Fungal pathogens *Nocardia* *Candida* *Aspergillus* spp.
B-cell defects	Selective IgA deficiency Common variable immunodeficiency Bruton X-linked agammaglobulinemia	Recurrent sinopulmonary infections Meningitis Osteomyelitis • Recurrent GI infections	Bacterial pathogens *Streptococcus pneumoniae* *Streptococcus pyogenes* *Staphylococcus aureus* (MSSA, MRSA) *Haemophilus* spp. *Pseudomonas* Viral pathogens Enterovirus Parasites *Giardia* *Cryptosporidium*
T-cell defects	Severe combined immunodeficiency DiGeorge syndrome	Recurrent pneumonia/ pneumonitis Failure to thrive Chronic mucocutaneous candidiasis	Bacterial pathogens Common Gram-positive and Gram-negative organisms Fungal pathogens *Pneumocystis jirovecii* *Candida* spp. *Nocardia* Viral pathogens Enterovirus Herpesviruses (CMV, EBV, VZV) Adenovirus
Complement defects	C6, C7, or C8 deficiency	Recurrent meningitis, sepsis	Bacterial pathogens *Neisseria meningitidis* *Streptococcus pneumoniae*

MSSA methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *spp.* species, *GI* gastrointestinal, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *VZV* varicella zoster virus

of infection such as typhlitis or a perirectal abscess, then the addition of metronidazole must be considered, as cefepime has no anaerobic coverage.

In patients with prolonged, profound neutropenia; those who are still febrile on broad-spectrum antimicrobial therapy for 96 or more hours; those with high-risk malignancy such as acute myelocytic leukemia, high-risk acute lymphocytic

leukemia; or those who have received high-dose corticosteroids, evaluation and treatment for invasive fungal infection must be considered. The Children's Oncology Group Guidelines recommend imaging of the chest and abdomen to look for a nidus of infection. However, they provide weak recommendations against the routine CT imaging of the sinuses without symptoms as there may be some nonspecific findings. Serum fungal biomarkers such as galactomannan and β-D-glucan are discouraged due to their poor positive and negative predictive values. Empiric antifungal coverage with echinocandins (e.g., caspofungin or micafungin) or liposomal amphotericin B should be started pending the results of a comprehensive evaluation. This regimen will cover most *Candida* species and many invasive molds such as *Aspergillus* species.

35.6.2 Hematopoietic Cell Transplant (HCT) Patients

Patients who receive hematopoietic cell transplantation (HCT), particularly those who receive allogeneic transplantation, are some of the most vulnerable hosts at risk for severe infections with opportunistic pathogens. Among the many significant risk factors for infection, most notable are the intensity of the pretransplant conditioning regimen including myeloablative regimens or total body irradiation; prolonged, profound neutropenia; underlying disease such as high-risk malignancy; pretransplant history of certain infections including CMV, HSV, EBV, and VZV in the recipient; higher degree of donor-recipient human leukocyte antigen (HLA) mismatch; and the presence of graft-versus-host disease (GVHD).

In the pre-engraftment period, HCT patients are essentially without a functioning bone marrow and therefore without a functioning immune system. The most common infections are bacterial and fungal infections given breakdown of mucosal barriers, presence of invasive lines, and persistent neutropenia (Table 35.3). Fever in these patients must be promptly evaluated with blood cultures and urine cultures; empiric antipseudomonal therapy such as cefepime, piperacillin-tazobactam, or carbapenem must be started similar to the high-risk oncology patients. The addition of vancomycin and aminoglycoside therapy can be considered in patients in the PICU with hemodynamic instability. Prolonged fevers must be evaluated for invasive fungal infections most commonly *Candida* species and molds such as *Aspergillus*.

Along with bacterial and fungal pathogens, during the pre-engraftment, engraftment (15–30 days posttransplant), and the early post-engraftment (30–100 days) periods, HCT patients are at high risk for respiratory failure and significant pneumonitis due to several respiratory viruses including RSV, influenza, and adenovirus. These viruses result in significant morbidity and mortality in these patients despite the use of antivirals such as inhaled ribavirin for RSV, oseltamivir for influenza, and cidofovir for adenovirus.

HCT patients are also at high risk for herpesvirus infections in the early post-engraftment and late post-engraftment (>100 days posttransplant) periods, the most overwhelming of which can be CMV pneumonitis and hepatitis. The highest-risk patients are those who are donor seronegative for CMV and recipient seropositive. The viruses in the herpesvirus family are unique in that after acquisition of the primary infection, the virus attains a latency phase and can reactivate when the opportunity presents. In HCT recipients who have had past exposure to CMV (recipient seropositive), CMV can be latent in the tissues. If the donor has never had any prior exposure to CMV (donor seronegative), then the newly engrafted donor immune system has no memory of controlling CMV infection. These patients are therefore at highest risk for developing disseminated infection with CMV. The diagnosis is made with elevated CMV viremia detected on serum PCR analysis; for pneumonitis, CMV

Special population:

- HCT patients who are donor negative and recipient positive for herpesviruses (i.e., CMV, EBV) are at highest risk of developing overwhelming infections with those viruses.

Table 35.3 Hematopoietic cell transplantation and risk of infection with the most common pathogens

Pre-engraftment	Engraftment (Days 15–30)	Early post-engraftment (Days 31–100)	Late post-engraftment (Day > 100)
Major risk factors Neutropenia Breakdown of skin and mucosal barrier Lymphopenia	*Major risk factors* Lymphopenia Hypogammaglobulinemia Acute GVHD	*Major risk factors* T-cell deficiency Hypogammaglobulinemia Acute GVHD	*Major risk factors* T-cell deficiency Chronic GVHD
Bacterial pathogens Gram-negative microbes GI streptococci (viridans streptococci) Staphylococci	*Bacterial pathogens* Gram-negative microbes Staphylococci GI streptococci[a] *Nocardia*	*Bacterial pathogens* Gram-negative microbes[a]	*Bacterial pathogens* Encapsulated bacteria
Fungal pathogens *Candida* spp. *Aspergillus*	*Fungal pathogens* *Aspergillus* *Pneumocystis jirovecii*	*Fungal pathogens* *Aspergillus* *Pneumocystis jirovecii*	*Fungal pathogens* *Aspergillus* *Pneumocystis jirovecii*
Viral pathogens Respiratory viruses GI viruses HSV	*Viral pathogens* CMV Adenovirus Respiratory viruses	*Viral pathogens* CMV EBV Respiratory viruses	*Viral pathogens* CMV VZV EBV

GVHD graft-versus-host disease, *GI* gastrointestinal, *HSV* herpes simplex virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *VZV* varicella zoster virus
[a]Less likely than pre-engraftment

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can be detected by PCR from bronchoalveolar lavage fluid. Intravenous ganciclovir is generally used as empiric therapy, and CMV-specific immunoglobulin (CMV Ig) may be used as an adjunct to antiviral therapy for CMV pneumonitis in pediatric HCT patients.

35.6.3 Solid Organ Transplant Patients

Solid organ transplant patients are at risk for severe infections due to the profound iatrogenic immunosuppression given to prevent rejection of the donor graft. Risk stratification is mainly based on the type of organ transplant (the lungs, heart, and intestines are at highest risk) as well as the degree and timing of induction immunosuppression. Induction with agents such as antithymocyte globulin (ATG), although important for preventing graft rejection, delays the normal return of functioning T-lymphocytes by several months. During this period, patients are at high risk for opportunistic infections. These patients are then started on a protracted course of daily immunosuppressive therapy (e.g., tacrolimus, mycophenolate mofetil). The risk of infection with certain organisms changes in the early, intermediate, and late posttransplant periods as the degree of immunosuppression eases (Table 35.4). However, if the patient suffers from rejection, high-dose immunosuppression may again be required. If that occurs, the patient is as vulnerable for opportunistic infections as in the immediate posttransplant period. Solid organ transplant patients with sepsis should be started on broad-spectrum empiric antimicrobial therapy applying similar strategies to those used in the febrile neutropenia and HCT patient populations; this is particularly true in the early posttransplant period when they are at risk for bacterial and fungal infections.

Special population:
- When solid organ transplant patients with rejection undergo re-induction with immunosuppression, the timeline of immune reconstitution is restarted as if it was day 0 of transplant.

Table 35.4 Solid organ transplantation and risk of infection with the most common pathogens

Posttransplant 0–1 month	Posttransplant 1–6 months	Posttransplant > 6 months
Increased risk for nosocomial infection Central line infection Wound dehiscence Surgical site infection	*Activation of donor-derived infection* *Period of continued intensive immunosuppression*	*Community-acquired infections* Pneumonia and UTI More common than nosocomial infection *Late viral reactivation off prophylaxis* *Depends on degree of immunosuppression*
Bacterial pathogens Gram-positive (including MRSA) Gram-negative (including pseudomonas) Bacteria colonizing the recipient (i.e., resistant pseudomonas in lung transplantation with cystic fibrosis)	*Bacterial pathogens*[a] Gram-positive microbes Gram-negative microbes	*Bacterial pathogens* *Streptococcus pneumoniae* *Staphylococcus aureus* Gram-negative microbes (UTI)
Fungal pathogens *Candida* species *Aspergillus*	*Fungal pathogens* *Pneumocystis jirovecii* (less likely with prophylaxis) *Cryptococcus* Endemic fungi	*Fungal pathogens* *Aspergillus* *Pneumocystis jirovecii* (without prophylaxis) Endemic fungi
Viral pathogens Respiratory viruses GI viruses HSV	*Viral pathogens* CMV (less likely with prophylaxis) Adenovirus EBV BK virus (renal transplant)	*Viral pathogens* EBV (PTLD) CMV BK virus (renal transplant) Respiratory viruses

UTI urinary tract infection, *MRSA* methicillin-resistant *Staphylococcus aureus*, *GI* gastrointestinal, *HSV* herpes simplex virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *PTLD* posttransplant lymphoproliferative disorder
[a]Less likely than 0–1 month posttransplant

Among solid organ patients, those that are donor seropositive and recipient seronegative are at highest risk for disseminated CMV and EBV infections. When the donor has a prior history of CMV infection (donor seropositive), the donor organ may potentially carry latent CMV. The recipient immune system is already impaired by significant immunosuppression and has no prior experience or memory of the virus. In such cases, CMV can cause an overwhelming infection unchecked by the recipient immune system. Therefore, solid organ transplant patients at high risk for CMV infection are placed on prolonged valganciclovir prophylaxis. CMV pneumonitis, especially in lung transplant patients, can be particularly devastating. As with HCT patients, the treatment for this condition is intravenous ganciclovir and adjunctive CMV Ig.

Unlike CMV, there is no effective antiviral for EBV. EBV infection in high-risk solid organ transplant (donor positive, recipient negative) and HCT (donor negative, recipient positive) patients can lead to posttransplant lymphoproliferative dis-

Special population:

- In contrast to HCT, solid organ transplant patients who are donor positive and recipient negative for herpesviruses (i.e., CMV, EBV) are at highest risk of developing overwhelming infections with those viruses.

order (PTLD), which is an unchecked proliferation of a clonal population of EBV-infected and immortalized B-cells. In solid organ transplant recipients, the EBV infection is generally a primary infection from its reservoir in the lymphocytes of the donor organ. Therefore, lung and intestine (organs with the largest burden of donor leukocytes) transplant patients are at highest risk of primary EBV infection. With suspicion for PTLD and rising EBV viremia, the initial treatment is reduction of immunosuppression to restore a cytotoxic T-cell response that can control the EBV infection. Second-line therapy includes anti-CD20 agents such as rituximab with or without chemotherapy. Antiviral prophylaxis either with acyclovir or ganciclovir is generally not effective. Strategies to prevent PTLD include serial viral load monitoring using PCR analysis in high-risk patients.

35.7 Less Common and/or Travel-Related Infections

35.7.1 Rickettsia

Rickettsial infections are transmitted via tick bites from a variety of different species and have specific epidemiologic risk factors to consider including travel to endemic regions (generally Southeastern United States and Northern Mexico) and animal and outdoor environment exposures. *Rickettsia rickettsii*, which causes Rocky Mountain spotted fever, results in a rapid clinical decline with a high mortality rate after the start of symptoms which include high fever, headache, myalgia, and, eventually, a palm and sole petechial rash. The early initiation of doxycycline should be started, *regardless of the age of the child*, as it can be lifesaving. Additional supportive care is usually required.

35.7.2 Viral Hemorrhagic Fevers

Overall, most viral hemorrhagic fever infections (e.g., Ebola, dengue, yellow fever, Lassa virus, hantavirus) are associated with recent travel to Africa, South America, or Asia although hantavirus is endemic in the southwestern United States. Patients often present with fever, petechial rash, edema, and shock. A rapid progression of DIC with multiorgan dysfunction develops resulting in hemorrhagic shock and in an inappropriate and/or unregulated immune response. Patients can be highly contagious, especially from contact with bodily fluids. The diagnosis is often made based on symptom and exposure histories, progression of symptoms, and PCR studies. Treatment is often supportive therapy, but intravenous ribavirin and novel antimicrobial therapies have been tried. Unlike other hemorrhagic fevers, Ebola requires strict airborne and contact isolation, until the patient can be transferred to a biocontainment facility. Supportive therapy is important as is in other shock states including fluid resuscitation and monitoring for DIC. Novel antimicrobial therapy is currently under investigation. In addition, given more recent global outbreaks of a number of viruses, vaccine research has also progressed substantially.

35.7.3 Malaria

Malaria is a parasitic infection with variable clinical phenotypes, caused by a number of different malaria species depending on the country of exposure. A recent or remote history of being in an endemic area should initiate an evaluation when patients present with fever and flu-like illness. In addition, patients may have more significant signs and symptoms including abdominal pain, gastrointestinal bleeding and/or obstruction, and severe headache with or without

meningeal signs or neurologic abnormalities. Anemia is expected, and additional laboratory abnormalities such as elevated hepatic enzymes, hyperbilirubinemia, thrombocytopenia, and renal insufficiency may occur. The diagnosis can be made via thick/thin smear with light microscopy, antigen-based testing, and/or molecular testing by PCR. If there is suspicion of an infection in the United States, healthcare providers should consult with local pediatric infectious diseases experts if available. If no in-person consultation is available, providers should call the CDC Malaria Hotline (770–488-7788). For severe infections, artemisinin combination therapy (ACT) plus primaquine should be initiated early, although ongoing primaquine doses depend on malarial species and glucose-6-phosphate dehydrogenase (G6PD) status. Treatment for patients with malaria in the United States should be guided in consultation with local experts and/or national (CDC) guidance. In the setting of high parasitemia with multiorgan dysfunction, an exchange transfusion along with antiparasitic therapy has been found to improve survival in endemic areas. Complications of hypoglycemia, seizures, increased intracranial pressure, and cerebral edema should be closely monitored. Fluid resuscitation is an important aspect of care, but aggressive fluid boluses have been associated with increased pediatric mortality.

Travel-related infections:
- CDC Malaria Hotline (770-488-7788) or Toll-free (855)856-4713

35.7.4 Tuberculosis (TB)

Mycobacterium tuberculosis is often an indolent organism causing primarily pulmonary disease. However, extrapulmonary manifestations also occur including meningitis, CNS tuberculomas, and vertebral body bone involvement. These extrapulmonary manifestations are particularly common in children and may be life-threatening. TB can also present as systemic disease infecting almost any organ in the human body. If suspicion arises for TB, the patient should be placed in a negative pressure room under airborne isolation. Testing options include tuberculin skin testing (PPD) and interferon gamma release assays (IGRA) from the blood. IGRA testing is less reliable in overwhelming acute TB infections and in infants and young children. Body fluid and/or tissue samples should be obtained whenever possible to utilize direct culture and molecular testing (PCR) for detection of TB. Due to the prolonged course of treatment, early involvement with the Department of Health and Pediatric Infectious Diseases experts will assist in optimal management strategies and to prevent development of mycobacterial resistance. In addition to initiating TB treatment, monitoring for other coinfections like HIV and close monitoring of nutritional status are important.

35.8 Summary

Life-threatening and life-limiting infections are not only a relatively common reason for admission to the PICU but also occur as a complication of other critical illnesses and conditions. The timely and effective evaluation and treatment of a critically ill child with infection holds the potential to increase survival and minimize morbidity. However, such care requires a sound understanding of the epidemiology and pathophysiology, careful attention to detail, and a systematic approach to the diagnosis and treatment of these infections. Specific history and physical exam findings may provide essential information regarding the most likely pathogen, the host immune status, and the source of the infectious process. Such information is pivotal to the initiation of the appropriate antimicrobial therapy in a timely and thoughtful manner (Table 35.5). This chapter provides an approach to the care of a variety of life-threatening infections in children. For each infectious process, the pathogenesis, potential organisms, and treatment nuances are described.

Table 35.5 Summary of approach to severe infections in children

A) Potential pathogens	
Infectious process	*Potential pathogens*
Sepsis Immunocompetent patients, non-neonates	MSSA, *Streptococcus pneumoniae*, +/– MRSA Urine sources consider *Escherichia coli*, *Klebsiella* species Less common organisms *Pseudomonas* *Enterococcus* *Salmonella species* Animal-related bacteria Food and water-borne pathogens
Sepsis Immunocompromised patients	MSSA, Pseudomonas, Gram-negative microbes, +/– MRSA Intra-abdominal nidus (typhlitis, perirectal abscess) Gram-negative microbes Anaerobes Concern for invasive fungal infection *Candida* species *Aspergillus* species
Toxic shock syndrome	MRSA, MSSA, *Streptococcus pyogenes*
Septic jugular vein thrombophlebitis (Lemierre syndrome)	*Fusobacterium necrophorum* *Fusobacterium nucleatum* Less common organisms *Staphylococcus aureus* *Streptococcus pyogenes* Other oral flora
Complicated pneumonia with empyema	*Staphylococcus aureus* (MSSA, MRSA) *Streptococcus pneumoniae* *Streptococcus pyogenes*
Neonatal sepsis (with or without meningitis)	Group B *Streptococcus* (*Streptococcus agalactiae*) *Escherichia coli* *Listeria monocytogenes* Possible HSV-1, HSV-2

Meningitis (>6 weeks of age and children)	*Streptococcus pneumoniae* *Neisseria meningitidis* *Haemophilus influenza* type B Possible HSV-1, HSV-2	
Brain abscess (immunocompetent patients)	*Streptococci species* *Streptococcus anginosus* *Streptococcus pneumoniae* *Staphylococcus aureus* (MSSA, MRSA) Anaerobes	
Necrotizing fasciitis	*Streptococcus pyogenes* *Staphylococcus aureus* (MSSA, MRSA) *Clostridium* species Anaerobes Gram-negative microbes Water contamination *Vibrio vulnificus* *Aeromonas hydrophila*	
B) Treatment options		
Infectious process	*Preferred empiric therapy*	*Alternative empiric therapy*
Sepsis Immunocompetent patients, non-neonates	Ceftriaxone + vancomycin Empiric coverage for other pathogens depends on History of resistant organisms Presence of devices Exposure history	Piperacillin-tazobactam + vancomycin OR Cefepime + metronidazole + vancomycin
Sepsis Immunocompromised patients	Cefepime + vancomycin +/– aminoglycoside in hemodynamically unstable patient For intra-abdominal source, consider addition of metronidazole to cefepime For empiric antifungal coverage, liposomal amphotericin B	Vancomycin + meropenem For intra-abdominal source, vancomycin + piperacillin-tazobactam For empiric antifungal coverage, caspofungin
Toxic shock syndrome	Vancomycin + beta-lactam (nafcillin or cefazolin) + clindamycin	If beta-lactam allergy Vancomycin + clindamycin

(continued)

Table 35.5 (continued)

Septic jugular vein thrombophlebitis (Lemierre syndrome)	Ampicillin-sulbactam Consider addition of vancomycin for MRSA	Piperacillin-tazobactam OR Ceftriaxone + metronidazole OR If beta-lactam allergy Levofloxacin + metronidazole Consider addition of vancomycin for MRSA
Complicated pneumonia with empyema	Clindamycin + ceftriaxone	Vancomycin + ceftriaxone
Neonatal sepsis (with or without meningitis)	Ampicillin + gentamicin (if no CSF pleocytosis) Ampicillin + cefotaxime[a] (with CSF pleocytosis) +/– Acyclovir (empiric use < 28 days of age) or with clinical suspicion	Ampicillin + cefotaxime[a], +/– vancomycin (severe sepsis) +/– Acyclovir (empiric use < 28 days of age) or with clinical suspicion
Meningitis (> 6 weeks of age and children)	Vancomycin + ceftriaxone +/– acyclovir if clinical presentation suggestive of HSV	
Brain abscess (immunocompetent patients)	Ceftriaxone + metronidazole +/– vancomycin with concern for MRSA or resistant *Streptococcus pneumoniae*	If beta-lactam allergy Levofloxacin + metronidazole + vancomycin
Necrotizing fasciitis	Vancomycin + piperacillin-tazobactam + clindamycin OR Vancomycin + meropenem + clindamycin Pathogen-specific considerations Group A Strep: Penicillin + clindamycin *Vibrio vulnificus*: Doxycycline + ceftriaxone *Aeromonas hydrophila*: Doxycycline + ceftriaxone or Doxycycline + ciprofloxacin	Vancomycin + ceftriaxone (or cefepime if pseudomonas risk) + metronidazole

MSSA methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *HSV* herpes simplex virus, *CSF* cerebrospinal fluid

[a]Alternatives with cefotaxime shortage: cefepime or ceftazidime

Review Questions

1. A 12-year-old male presents with temperature of 39.5 °C, heart rate 150 bpm, blood pressure 82/40 mmHg, and increased pain of his right arm after a possible puncture wound suffered 5 days ago. The child is crying in pain upon palpation of the entire arm, but physical exam reveals only mild erythema at the site of the previous puncture wound with scant discharge from the opening. Given the concern for necrotizing fasciitis, vancomycin and piperacillin-tazobactam are administered. In addition to administering a fluid bolus of 20 mL/kg, what is the most appropriate next step in the management of this child?
   (a) Immediate surgical exploration of the right arm
   (b) Magnetic resonance imaging (MRI) of the right arm
   (c) Radiograph of the right arm
   (d) Serum antibody testing for *Clostridium perfringens*

2. A 4-month-old unvaccinated female presents with 2 days of fever (current temperature 40.1 °C), heart rate 196 bpm, respiratory rate 42 bpm, and blood pressure 70/35 mmHg. She is irritable and is noted to have a bulging fontanelle on clinical exam. A lumbar puncture is performed and analysis of the cerebrospinal fluid (CSF) reveals:
   White blood cell: 4200 cells/μL with 90% neutrophils and 10% monocytes
   Red blood cell: 5 cells/μL
   Glucose: 12 mg/dL
   Protein: 525 mg/dL
   Gram stain: Many neutrophils and Gram-positive diplococci
   She is treated with vancomycin and ceftriaxone. Besides considering neuroimaging, what other testing is necessary to counsel the family regarding the patient's prognosis?
   (a) Auditory brainstem response test
   (b) Neutrophilic function tests
   (c) Otoacoustic emission test
   (d) Repeat lumbar puncture and CSF analysis

3. A 5-year-old female s/p deceased donor renal transplant (DDRT) 3 months ago presents with fever for 2 days (current temperature 39.2 °C), heart rate 136 bpm, respiratory rate 24 bpm, and blood pressure 122/82 mmHg. Her creatinine is 2.4 mg/dL which is double of her baseline and concerning for graft rejection. While reviewing donor and recipient serology for cytomegalovirus (CMV), which of the following would place the patient at highest risk for CMV infection?
   (a) CMV donor negative, recipient negative
   (b) CMV donor negative, recipient positive
   (c) CMV donor positive, recipient negative
   (d) CMV donor positive, recipient positive

4. A 3-year-old male with trisomy 21 and unrepaired atrioventricular canal defect presents with fever of 2-week duration. His vital signs on admission reveal temperature 39.7 °C, heart rate 171 bpm, respiratory rate 28 bpm, and blood pressure 84/33 mmHg. Clinical exam reveals a small, somnolent obese male with facial features consistent with his diagnosis of trisomy 21. His breath sounds reveal scattered rales and transmitted upper airway sounds. A murmur is readily appreciated on clinical exam, although the "isolation room" stethoscope makes it difficult to further characterize. He has a small painful lesion at the end of his right large toe. He is initially started on broad-spectrum antimicrobial therapy consisting

of vancomycin and ceftriaxone. His transthoracic echocardiogram is structurally unchanged from baseline with no evidence of an intracardiac mass, vegetation, or abscess and no new valvular regurgitation. His initial blood culture grows a viridans group *Streptococcus*. Which of the following would most strongly support a definite diagnosis of infectious endocarditis in this child based on the Modified Duke Criteria?

(a) A subsequent (≥12 h later) blood culture positive for viridans group *Streptococcus*
(b) Documentation of dental caries on panoramic radiograph
(c) Persistent fever for the ensuing 48 h despite appropriate antimicrobial therapy
(d) The diagnosis of infective endocarditis cannot be made with the provided echocardiographic data

5. A 5-year-old male presents with high fevers of 5-day duration and an altered mental status. Vital signs on admission reveal temperature 40.3 °C, heart rate 172 bpm, respiratory rate 30 bpm, and blood pressure 75/38 mmHg. Clinical exam reveals a well-nourished and well-developed child. He is obtunded but does moan and sluggishly withdraw to noxious stimulation. He will not open his eyes. He is tachypneic, but his breath sounds are relatively clear and equal. He is tachycardic with a regular rhythm and a soft systolic murmur. His abdomen is soft and non-distended. He has a petechial rash on the bottom of his feet. He received a fluid bolus and was intubated upon arrival to the PICU for airway management. Besides starting vancomycin and ceftriaxone at meningitic dosing, what other steps should be taken immediately?

(a) Assess serum for *Rickettsia* utilizing polymerase chain reaction testing and start dexamethasone after the first dose of antibiotics.
(b) Start clindamycin immediately and then measure serum *Rickettsia* antibody levels.
(c) Start doxycycline immediately and then measure serum *Rickettsia* antibody levels.
(d) Start metronidazole immediately and then assess serum for *Rickettsia* utilizing polymerase chain reaction testing.

Answers

1. *A*
2. *A*
3. *C*
4. *A*
5. *C*

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Multiple Organ Dysfunction Syndrome

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Contents

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Learning Objectives

- To recognize the clinical scenarios that may lead to the development of multiple organ dysfunction syndrome
- To describe the proposed cellular mechanisms that lead to multiple organ dysfunction syndrome in response to a pathologic stimulus and attendant organ pathology
- To understand the attendant organ pathophysiology in a patient experiencing multiple organ dysfunction syndrome
- To plan a course of therapy for a patient with multiple organ dysfunction syndrome
- To review reported outcomes, and the criteria used to predict them, among patients with multiple organ dysfunction syndrome

36.1 Introduction

All organs are not created equal – in terms of the effect of their dysfunction on patient outcome.

Multiple organ dysfunction syndrome (MODS) is the final common pathway that results from a variety of insults resulting in widespread endothelial dysfunction and organ injury. Although first described in the literature over four decades ago, it still can only be described as a syndrome, a constellation of signs and symptoms that consistently occur together, have a common pathophysiologic mechanism, and have a predictable outcome. In pediatrics, MODS is most commonly related to sepsis and the resultant inflammation. However, it also frequently occurs in a number of other conditions including massive hemorrhage and/or multiple trauma. Upward of 75% of patients admitted to surgical intensive care units who die have their cause of death listed as "multiple organ system failure." The terminology describing multiple organ dysfunction syndrome and failure has evolved over time. In 1992, the American College of Chest Physicians/Society of Critical Care Medicine Consensus statement described the "multiple organ dysfunction syndrome" as a continuum of organ compromise. In 2005, an international pediatric sepsis consensus conference reviewed and revised the diagnostic criteria. In 2015, the National Institutes of Health convened a Pediatric Multiple Organ Dysfunction Syndrome Workshop consisting of experts in the field with the goal to identify knowledge gaps and research priorities. Although multiple terms have been used throughout the published literature to describe this condition including "multiple organ failure" and "multiple organ system failure," multiple organ dysfunction syndrome appears to be the most commonly accepted term at this time.

This chapter will outline the epidemiology and clinical presentation of pediatric patients with MODS. Since the basic pathophysiologic mechanisms leading to MODS are those described amply in the chapters on inflammation, the endothelium, sepsis, and acute respiratory distress syndrome, the reader is referred to those chapters for more detail. The methods of characterizing organ dysfunction in pediatric MODS will be reviewed along with elements of treatment and supportive care. The prevention of MODS relies on early recognition of risk factors and triggering conditions with aggressive treatment of these underlying conditions *before* organ injury develops. The care of patients with MODS is primarily supportive. Subtypes of sepsis-induced multiple organ failure have been characterized, and therapeutic considerations for each will be outlined.

36.2 Epidemiology

Dr. Arthur Baue, a surgeon, first proposed the concept of multiple, progressive, or sequential organ system failure as a syndrome in the mid-1970s. It was a decade later before the first set of diagnostic criteria were reported

Table 36.1 Diagnostic criteria of multiple organ dysfunction syndrome

Organ system	Criteria
Cardiovascular	*If after 40 ml/kg intravenous fluid bolus over one hour* Hypotension (<5% for age) or SBP < 2 SD below normal for age *OR* the need for any vasoactive infusion to maintain normal blood pressure *OR* two of the following:
	Unexplained metabolic acidosis (base deficit >5.0 mEq/L)
	Increased lactate level (>2 times upper limit of normal)
	Oliguria or anuria (<0.5 mL/kg/hour)
	Prolonged capillary refill (>5 seconds)
	Core to peripheral temperature difference (>3°)
Respiratory	PaO_2/FiO_2 < 300 Torr (without cyanotic heart disease or pre-existing lung disease)
	$PaCO_2$ > 65 Torr or 20 mm Hg above baseline
	Need for >50% FiO_2 to maintain oxygen saturations ≥92%
	Need for nonelective invasive or noninvasive ventilation
Neurologic	Glasgow Coma Scale (GCS) ≤ 11
	Acute change in mental status (decrease in GCS ≥ 3 points from abnormal baseline)
Hematologic	Platelet count <80,000/cubic mL (or 50% reduction in chronic patient)
	International normalized ratio (INR) <2
Renal	Serum creatinine ≥2 times the upper limit of normal for age or doubling of baseline creatinine
Hepatic	Total serum bilirubin >4 mg/dL (excluding newborns)
	Alanine transaminase (ALT) 2× upper limit of normal for age

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by Wilkinson in 1987, and Proulx adjusted the definitions in 1996. In 2005, Goldstein revised the diagnostic criteria (Table 36.1). In 2015, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development convened a Multiple Organ Dysfunction Syndrome Workshop. Robust diagnostic criteria are important in accurately establishing both the incidence and prevalence of MODS and in identifying progressive organ dysfunction.

The incidence of MODS in children admitted to the pediatric intensive care unit (PICU) across all diagnoses is reported to range between 6% and 57% in published studies over the last three decades, encompassing the varied sets of diagnostic criteria. Sepsis is the dominant cause of MODS in children, with the incidence ranging between 17 and 73% in published reports. Other causes

of MODS include burns, trauma, congenital heart disease, and hematopoietic cell transplantation. The wide range of reported incidence rates of MODS is likely influenced by the varied definitions used over time.

36.3 Clinical Presentation

MODS is considered to represent the end result, or the most severe end of a spectrum, that is characterized by a systemic inflammatory process (e.g., sepsis in the presence of an infection) or simply the systemic inflammatory response syndrome (SIRS) in the absence of infection. However, many patients meet the criteria of primary MODS on presentation to the PICU, either due to direct organ injury or pre-hospitalization manifestations of progressive organ dysfunction. Primary MODS is defined as two simultaneous dysfunctional organs within a week of PICU admission and without subsequent additional organ dysfunction. The patient who develops failure of more than one organ may have experienced a variety of insults, either overwhelming infection, hemorrhage (with or without a traumatic injury), or other conditions associated with systemic inflammation.

The clinical presentation of MODS can vary tremendously depending upon the underlying cause. Five inflammatory phenotypes have been described in the setting of sepsis, inflammation, and multiple organ failure. These include:

- *Thrombocytopenia-associated multiple organ failure (TAMOF)* which is characterized by reduced ADAMTS13 activity (< 57% of controls) which results in platelet clots, endothelial dysfunction, and a thrombotic microangiopathy. It is clinically manifested by new-onset thrombocytopenia, elevated lactate dehydrogenase levels, and acute kidney injury.
- *Immunoparalysis-associated multiple organ failure* can impact innate and adaptive immune function and is characterized by lymphopenia, a decreased *ex vivo* whole blood tumor necrosis factor-alpha response to endotoxin, decreased monocyte HLA-DR expression, and increased expression of inhibitory cell surface molecules such as PD-1. In addition to organ failure, it may be clinically manifested by an inability to clear bacterial or fungal infections.
- *Sequential multiple organ failure* is characterized by dysfunction of natural killer cells and cytotoxic T-lymphocytes resulting in disrupted destruction of viruses, cancer cells, and activated immune cells leading to unchecked viremia, lymphoproliferation, release of soluble Fas ligand (sFasL), hemophagocytosis, and sFasL-mediated liver injury. Uncontrolled inflammation occurs secondary to the inability to eliminate viruses or to induce apoptosis of activated immune cells. Clinically, it manifests with respiratory failure followed days later by new-onset liver dysfunction.
- *Critical pertussis-associated multiple organ failure (hyperleukocytosis and pulmonary hypertension-associated multiple organ failure)* is characterized by margination of neutrophils and lymphocytes leading to endothelial injury and cellular plugging of pulmonary arterioles, resulting in cardiopulmonary collapse.
- *Macrophage activation syndrome* is proposed to represent a final common pathway of uncontrolled inflammation. It is associated with endothelial disruption, macrophage production, disseminated intravascular coagulation, hepatobiliary dysfunction, and hyperferritinemia.

Shock with its attendant compromise in effective substrate delivery appears to occur commonly in association with these various perturbations. Thus, early aggressive resuscitation to restore oxygen delivery to the tissues in a timely manner is crucial as this has been well documented to improve outcomes and decrease the likelihood of progressing to MODS. Such an approach is now integral to evidence-based guidelines for the treatment of septic shock. However, in the patients who progress to multiple organ failure, the resuscitation phase is followed by a period of metabolic derangement characterized by temperature dysregulation, tachycardia, encephalopathy, acute kidney injury, and coagulation abnormalities. Despite aggressive support, many of these patients succumb to progressive organ dysfunction; the survivors often require prolonged recovery. The clinical presentation by individual organ system is described in the following section.

The clinical presentation of MODS can vary tremendously depending upon the underlying cause with multiple inflammatory phenotypes described in the setting of sepsis.

36.3.1 Cardiovascular

Cardiovascular dysfunction is a common component of MODS. This may occur as a result of one or more of several mechanisms. First, the heart may suffer primary dysfunction in the presence of myocardial depressant factors (e.g., interleukin-6 (IL-6) in the setting of meningococcal sepsis). Second, the increased metabolic demands of systemic inflammation with widespread endothelial injury, attendant interstitial edema, and reduced effective circulating volume can result in an inadequate oxygen delivery to meet the metabolic demands of the body characterized clinically by tachycardia. Interleukins and other vasoactive substances may cause vasodilatation and compensatory responses to maintain perfusion to vital organs. Additionally, the concomitant need for mechanical ventilation has competing effects on the heart. Although the positive intrathoracic pressure may decrease systemic afterload, the positive end-expiratory pressure may impede venous return, resulting in decreased preload and a decrease in cardiac output. Dysrhythmias may result from ischemic injury or from metabolic derangements related to potassium and calcium. The balance between the sympathetic and parasympathetic systems may be altered in the setting of multiple organ dysfunction. This is mediated by several pathways, including the pulmonary stretch receptors, central and peripheral chemoreceptors, and arterial baroreceptors. Decreased heart rate variability predicts a higher severity of MODS, subsequent deterioration, and death. Predictive modeling of heart rate variability is an emerging area of study in the field.

36.3.2 Respiratory

The paramount finding in patients with respiratory compromise is the failure of normal gas exchange that occurs in the presence of multiple pathogenic mechanisms. Acute lung injury (ALI) is associated with interstitial and alveolar edema, promoting atelectasis and ventilation-perfusion inequality, and hypoxemia. Acute respiratory distress syndrome (ARDS) represents progression of the lung injury. The features of pediatric ARDS are discussed fully in another chapter in this text (► Chap. 11).

36.3.3 Neurologic

The first manifestation of neurologic injury in patients with MODS is an alteration in the level of consciousness. Although the exact pathogenesis is not defined, it is likely due in part to impairment of cerebral perfusion, inflammation, and associated metabolic abnormalities. Additionally, the

The first manifestation of neurologic injury in the population of patients with MODS is an alteration in the level of consciousness.

neurologic assessment in pediatric MODS is complicated by the common need for sedatives, analgesics, and, at times, neuromuscular blockade. The brain architecture is usually found to be preserved on autopsy in those dying with MODS, and computerized tomography may reveal the presence of cerebral atrophy in those with prolonged illness. Patients remain at risk for secondary insults including ischemic/hemorrhagic complications associated with abnormal coagulation parameters and hemodynamic perturbations as well as prolonged sedation in the presence of hepatic dysfunction. Depletion of vital nutrients can predispose patients to demyelination syndromes. A well-described phenomenon in later stages is the entity of *critical illness polyneuropathy*, manifest clinically as weakness and inability to wean from mechanical ventilatory support, and electromyography revealing decreased sensory action potential amplitude.

36.3.4 Gastrointestinal

The release of toxic gut-derived substances into the mesenteric lymph, intestinal permeability to bacterial and/or endotoxin translocation, and alterations in the intestinal microbiome may all contribute to MODS.

Pediatric MODS may also be associated with several aberrations of gastrointestinal function. In fact, all components of the gut – the epithelium, the immune system, and the microbiome – may be impacted by critical illness, triggering a pathologic host response leading to MODS. For example, preclinical work has suggested that the release of toxic gut-derived substances into the mesenteric lymph may produce distant organ injury. In addition, intestinal permeability to bacterial and/or endotoxin translocation from mucosal ischemia in shock states has long been hypothesized to be a primary mechanism for systemic disease. Further, recent evidence supports the concept that the intestinal microbiome is also a contributor of pathology. Microbiome diversity was associated with improved outcomes in adults following hematopoietic cell transplantation. Fecal microbiota transplants have a higher cure rate of *Clostridium difficile* infections compared to oral vancomycin. The methods by which the microbiome is optimized remain a focus of ongoing investigation.

Hepatic dysfunction in MODS is usually characterized by elevated serum bilirubin levels.

Hepatic dysfunction, usually characterized by elevated serum bilirubin levels, represents an aberration of the gastrointestinal system frequently encountered in MODS. A period of hypotension can result in hepatocellular injury followed by significant elevations in transaminases. Moreover, the gallbladder may also be affected by hypotensive states and, in rare cases, become necrotic. Gallstones or sludge may be found on ultrasound evaluation.

An ileus may result from a variety of factors including infection, electrolyte disturbances, and narcotic infusions. Pancreatitis can either be the cause of multiple organ failure or complicated by its presence. Amylase and lipase levels should be screened for in the setting of MODS. Gastrointestinal bleeding may result from or be potentiated by stress ulceration, prolonged nasogastric tube placement, and/or existing coagulopathy.

Diarrhea may result from bacterial overgrowth states, infection with commensal or opportunistic organisms, or the vigorous use of cathartic agents. Fluid losses can be severe and may require volume replacement especially in the younger child. Voluminous stool output may also predispose a patient to skin breakdown near the anus and buttocks, providing a portal of entry for organisms that may result in an additional insult to an already debilitated patient. Alternatively, the use of narcotic infusions may result in constipation, sometimes requiring cathartic agents or manual decompression.

36.3.5 Hematologic

Coagulopathy is a common finding in the patient with MODS. This may result from liver injury, dilutional states, overwhelming infection, and/or disseminated intravascular coagulation.

The presence of multiple organ failure can promote a full spectrum of hematologic aberrations, as can be inferred from the multiple criteria in ◘ Table 36.1. Complete marrow failure may accompany overwhelming bacterial or viral infections. The leukocyte count may be either elevated or depressed. Anemia may be present; aggressive blood drawing practice, particularly in small patients, should be monitored and is a common cause of iatrogenic anemia. Thrombocytopenia may be the presenting feature of infection and/or a component of a consumptive coagulopathy. Coagulopathy is a common finding in the patient with multiple organ failure. This may result from liver injury, dilutional states, or overwhelming infection. Clotting factors may be depleted in patients who have received large-volume fluid resuscitation or blood product replacement. In addition, there is accumulating evidence that the coagulation cascades play integral roles in the initiation and propagation of the inflammatory response. Disseminated intravascular coagulation is also common in patients with MODS and is described in detail in ▶ Chap. 38.

36.3.6 Renal

Acute kidney injury and renal failure are frequently observed in the patient with MODS. Renal failure ensues when the kidney is unable to excrete nitrogenous wastes and maintain fluid and electrolyte balance. Oliguria and azotemia result, requiring administration of diuretics or continuous renal replacement therapy. Fluid resuscitation that occurs in the setting of shock may result in volume overload. This may be problematic as the amount of fluid overload has been found to be an independent risk factor for death; as little as 10% fluid overload has been associated with an increased risk of mortality. In survivors, greater than 20% overload is associated with six times greater length of mechanical ventilation than those with less volume overload. The time to initiation of continuous renal replacement therapy (CRRT) has similarly been found to be an independent predictor of mortality with some data suggesting that every hour delay is associated with a 1% increase in mortality.

36.3.7 Other Systems

Many patients with MODS will experience hyperglycemia.

Although typically not considered as "organs" to meet criteria for MODS, other critical regulatory systems are often affected. Patients with MODS may experience dramatic alterations in blood glucose levels. The neonate with suboptimal glycogen stores may present with hypoglycemia. Many patients with MODS will experience hyperglycemia; up to 50% of previously healthy patients and almost all diabetic patients experience this complication. Proposed mechanisms include insulin resistance, relative insulin deficiency, and increased levels of counter-regulatory hormones. There is some concern that hyperglycemia may be related to a worse outcome in patients with sepsis and MODS. Patients with a history of steroid use, as well as others, may be at risk for adrenal insufficiency. Therefore, random cortisol sampling or ACTH-stimulation testing may be useful in this setting.

The skin is the largest organ of the body; it is important in both temperature regulation and as a barrier to infection. The skin dissipates heat quickly. In the infant or patient who has sustained trauma, burns, or an operative procedure, resultant hypothermia can promote coagulopathy and suboptimal

perfusion. Prolonged recumbency may facilitate the development of decubitus ulcers. The incidence of this complication is reported to be as high as 10% in some critically ill populations. Despite aggressive intervention, these wounds can become infected, possibly leading to systemic bacteremia, cellulitis, and/or osteomyelitis, all poorly tolerated in the already severely compromised patient. Meticulous attention to skin care may decrease these preventable complications.

The musculoskeletal system is affected in patients with multiple organ failure. Trauma and burn victims may develop rhabdomyolysis, which may quickly result in pigment nephropathy and acute kidney injury. Critical illness myopathy is another musculoskeletal condition associated with MODS. Prolonged bedrest, inadequate nutrition, neuromuscular blockade, and steroid use may all place a patient at risk for critical illness myopathy. The diagnosis may be confirmed by electromyography or muscle biopsy, which may reveal low compound muscle action potentials or Type II atrophy, respectively. Patients experiencing MODS are likely to benefit from early mobility as part of a comprehensive bundle to optimize recovery.

36.4 Outcomes and Predictors of Outcome

The PELOD score is a valid method of quantifying pediatric MODS.

The earliest descriptions of pediatric MODS highlighted the increased mortality risk that roughly correlated with the number of failed organs. The science of predictive modeling has been applied in developing the Pediatric Logistic Organ Dysfunction (PELOD) score, by assigning weighted scores based on degrees of different organ dysfunction. This score has been validated and offers clinicians and researchers a meaningful method of quantifying the degree of organ dysfunction. This score was further assessed in an unselected multicenter PICU population, in conjunction with the diagnostic categories of SIRS, sepsis, severe sepsis, and septic shock. The study not only validated the predictive value of the PELOD score but also demonstrated that the presence or absence – and severity – of the septic state dramatically alters mortality risk. For example, an increase of the PELOD score by 10 points in children without SIRS was associated with a hazard ratio of death of 2.5. In contrast, an increase of the PELOD score by 10 points in children with septic shock was associated with a hazard ratio of death of 81.5 (◘ Fig. 36.1). An updated PELOD score (PELOD-2) has been developed, validated, and published in 2013. It differs from the original PELOD in that mean arterial blood pressure and lactatemia have replaced heart rate and systolic blood pressure in the cardiovascular section, hepatic dysfunction has been excluded, and it now represents a continuous scale. The PELOD-2 score is in the public domain to be used for clinical research and is reproduced in ◘ Table 36.2.

The PELOD (PELOD-2) score utilizes the most abnormal values during the entire PICU stay; the daily PELOD (*d*PELOD) uses the most abnormal value for a 24-h period. For the dPELOD, when a variable is not measured, it is assumed to be either identical to the last measurement (if the physician considers that the value of the variable did not change) or normal (if the physician considers that the value of the variable is normal).

Given the difficulty of achieving adequate sample size to demonstrate differences in mortality in PICU clinical trials, organ dysfunction scores are often used as proxy outcome measures in lieu of mortality for these studies. The concept of *new and progressive MODS* (NPMODS) is commonly used as an

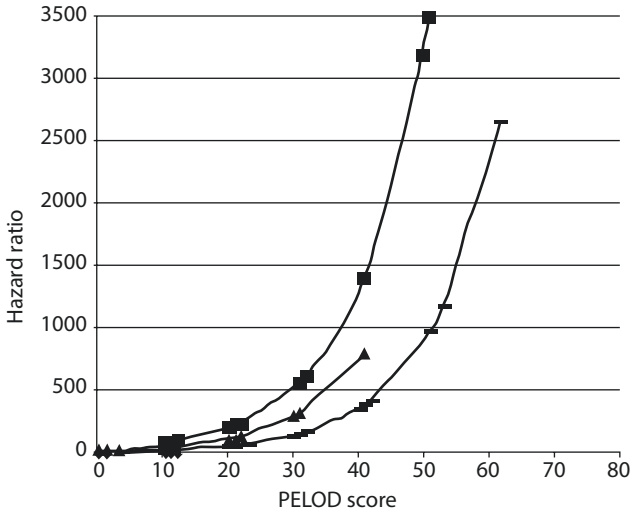

Fig. 36.1 Observed cumulative hazard ratios (HR) of death of the PELOD score and the diagnostic category of septic state. The figure depicts the observed cumulative hazard ratios (HR) of death of the PELOD score (which may range from 0 to 71) and the diagnostic category of septic state in the study population of 593 children consecutively admitted to a participating PICU. The HR of death is calculated by multiplying HR of the Pediatric Logistic Organ Dysfunction (PELOD) score ($1.096^{\text{PELOD score}}$) by HR of diagnostic category: no systemic inflammatory response syndrome (SIRS) (*diamond*); SIRS, sepsis (*dash*); severe sepsis (*triangle*); and septic shock (*square*). The subset of patients without SIRS depicted by the diamonds had low PELOD scores and low HR of death. Thus, they are depicted in the lower left side of the graph. (Reprinted with permission of the American Thoracic Society. Copyright © 2020 American Thoracic Society (Leclerc et al. 2005))

outcome variable in pediatric critical care clinical studies. NPMODS is defined as the proportion of patients who die within a study period or who develop new or progressive MODS. *New MODS* is a term used to describe patients who have no or only single organ dysfunction at the start of analysis (e.g., PICU admission or study randomization) and who develop two or more concurrent organ dysfunctions at any time during the study period (e.g., PICU discharge or study termination). Patients with MODS at the start of analysis (e.g., PICU admission or study randomization) can develop *progressive MODS* which is defined as death or the development of at least one additional concurrent organ dysfunction at any point during the study period.

In addition to PELOD, there are other scores that are used to identify organ system failure and severity. The Pediatric Multiple Organ Dysfunction Score (P-MODS), the Pediatric Sequential Organ Failure Assessment (P-SOFA), the Organ Failure Index (OFI), and the organ failure-free days represent but just a few of those that have been used. In addition, efforts to link circulating cytokine levels to predict organ injury and outcome in sepsis have been evaluated. Higher admission procalcitonin and tumor necrosis factor-alpha levels have been demonstrated among nonsurvivors of septic shock. Similarly, the lack of a decline in procalcitonin levels portends a significantly higher mortality rate. At this time, PELOD and other MODS scores serve as a measure of morbidity and severity of illness and not as a predictor of mortality. As such, they are not intended as replacement for the prognostic scoring systems designed and validated to predict the risk of death upon patient admission such as the Pediatric Risk of Mortality III (PRISM III) or Pediatric Index of Mortality-2 (PIM-2).

Table 36.2 Pediatric Logistic Organ Dysfunction-2 score

Organ dysfunctions and variables[a]	Points by severity levels						
	0	1	2	3	4	5	6
Neurologic[b]							
Glasgow Coma Score	≥11	5–10			3–4		
Pupillary reaction	Both reactive					Both fixed	
Cardiovascular							
Lactatemia (mmol/L)	<5.0	5.0–10.9			≥11.0		
Mean arterial pressure (mm Hg)							
0 to <1 month	≥46		31–45	17–30			≤16
1–11 months	≥55		39–54	25–38			≤24
12–23 months	≥60		44–59	31–43			≤30
24–59 months	≥62		46–61	32–44			≤31
60–143 months	≥65		49–64	36–48			≤35
≥ 144 months	≥67		52–66	38–51			≤37
Renal							
Creatinine (μmol/L)*							
0 to <1 month	≤69		≥70				
1–11 months	≤22		≥23				
12–23 months	≤34		≥35				
24–59 months	≤50		≥51				
60–143 months	≤58		≥59				
≥ 144 months	≤92		≥93				
Respiratory[d]							
PaO_2 (mm Hg)/FiO_2	≥ 61		≤60				
$PaCO_2$ (mm Hg)	≤ 58	59–94		≥95			
Invasive ventilation	No			Yes			
Hematologic							
WBC count (×109/L)	>2		≤2				
Platelets (×109/L)	≥142	77–141	≤76				

Logit (mortality) = −6.61 + 0.47 × PELOD-2 score
Probability of death = 1/(1 + exp. [−logit(mortality)])
Adapted from Leteurtre et al. (2013)

[a]All variables must be collected, but measurements can be done only if justified by the patient's clinical status. If a variable is not measured, it should be considered normal. If a variable is measured more than once in a 24-h period, the worst value is used in calculating the score. *PaO_2* arterial partial pressure of oxygen; *FiO_2* fraction of inspired oxygen; *$PaCO_2$* arterial partial pressure of carbon dioxide

[b]Neurologic dysfunction: Glasgow Coma Score: use the lowest value. If the patient is sedated, record the estimated Glasgow Coma Score before sedation

Assess only patients with known or suspected acute central nervous system disease. Pupillary reactions: nonreactive pupils must be >3 mm. Do not assess after iatrogenic pupillary dilatation

[c]Cardiovascular: Do not assess the mean arterial pressure during crying or iatrogenic agitation

[d]Respiratory dysfunction: PaO_2: use arterial measurement only. PaO_2/FiO_2 ratio is considered normal in children with cyanotic heart disease. $PaCO_2$ can be measured from arterial, capillary, or venous samples. Invasive ventilation: the use of mask ventilation is not considered invasive ventilation

To convert μmol/L to mg/dL, multiply by 0.0113

36.5 Cellular Mechanisms and Pathology

Altered permeability of the endothelium, resulting in interstitial edema and microcirculatory derangement from microvascular thrombosis, may result in local tissue cellular dysoxia and necrosis.

MODS can be viewed as the end-organ injury from the systemic inflammation that is initiated in SIRS or sepsis. In brief, a variety of stimuli can trigger an inflammatory cascade, initiated by cytokines (tumor necrosis factor-alpha, interleukin-1 (IL-1), etc.) from neutrophils and activated macrophages. The process is propagated by additional components such as platelet-activating factor and interferon gamma triggering the release of secondary mediators, arachidonic acid metabolites, and nitric oxide, by endothelial cells. Altered permeability of the endothelium, resulting in interstitial edema and microcirculatory derangement from microvascular thrombosis, may result in local tissue cellular dysoxia and necrosis. Organ involvement in MODS is characterized by edema, neutrophil infiltration, and microvascular thrombosis. Additionally, increased evidence of programmed cell death, apoptosis, has been noted in splenic lymphocytes and colonic epithelium.

36.6 Therapy

Meticulous supportive care remains the mainstay of treatment for pediatric MODS patients.

The mainstay of therapy in MODS is treatment of the inciting event that led to systemic compromise. Prevention of further insults by meticulous supportive care is paramount in promoting recovery of the affected systems.

36.6.1 Supportive Care in Multiple Organ Dysfunction Syndrome (MODS)

Once a patient has developed MODS, supportive care of affected organ systems is essential. The anticipation and prevention of additional complications improves the likelihood of survival and optimal outcome. Examples of such prevention techniques are summarized in ◘ Table 36.3 and described below.

The neurologic sequelae that MODS patients experience may be in part due to therapeutic measures designed to promote comfort and facilitate care, such as deep sedation, analgesia, and neuromuscular blockade. Critical illness myopathy may occur as a consequence of prolonged infusion of neuromuscular blocking agents, especially when coupled with corticosteroids or aminoglycoside antibiotics. Although titration may not prevent this complication, patients receiving neuromuscular blockade should be assessed frequently for the degree of blockade utilizing train-of-four monitoring (► Chap. 23) or intermittent medication cessation to reduce the risk of excessive dosage. In addition, many patients develop tolerance to sedative and analgesic infusions; abrupt withdrawal of these medications may predispose a patient to withdrawal symptoms of diarrhea, agitation, and, occasionally, seizures. Anticipation and initiation of a scheduled taper may mitigate these undesirable events. Any abrupt change in neurologic status warrants full evaluation, including brain imaging and, if safe and feasible, lumbar puncture. Patients who receive prolonged benzodiazepine infusions are at risk for the development of delirium. Patients who survive their initial insult are likely to benefit from measures to improve sleep and awareness. Long-term cognitive follow-up is an important area of study in patients who survive prolonged intensive care unit stays. A recent publication demonstrated that nearly one-quarter of children surviving community-acquired sepsis experience a clinically significant deterioration in health-related quality of life.

Cardiovascular manifestations of multiple organ failure result from both the disease process itself and therapeutic measures and procedures used during the hospitalization. Many patients with MODS require inotropic and/or vaso-

Table 36.3 Supportive care strategies in pediatric multiple organ dysfunction syndrome (MODS)

System	Treatment
Neurologic	Interruption of sedative and neuromuscular blockade infusions
Cardiovascular	Titration to optimize oxygen delivery
Respiratory	Adequate gas exchange, minimize risk of oxygen toxicity and baro-/volutrauma, prevention of ventilator-associated conditions
Gastrointestinal	Prevention of stress ulceration, early feeding when appropriate
Renal	Consideration of renal replacement therapy to treat/prevent fluid overload and allow for administration of adequate caloric intake
Endocrine	Maintain euglycemia, high index of suspicion for adrenal insufficiency
Immune	Adjustment of immunosuppressive agents
Infectious	Appropriate antimicrobials/anti-infectives, strict handwashing by caregivers, meticulous attention to aseptic technique in insertion/maintenance of intravascular catheters
Hematologic	Judicious use of blood products, consideration of granulocyte macrophage colony-stimulating factor
Musculoskeletal/ integumentary	Prevention of skin breakdown, aggressive therapy of decubitus ulcers, physical therapy to prevent muscle wasting, early mobility

active infusions. These should be initiated after adequate volume resuscitation has occurred. Central venous pressure monitoring may assist in optimizing intravascular volume. Maintaining superior vena cava oxygen saturations ($ScvO_2$) > 70% has been associated with improved outcomes in pediatric patients with septic shock. As with all invasive maneuvers, the risks and benefits must be carefully balanced. Dysrhythmias may result from the presence of a catheter in or near the right atrium or from electrolyte disturbances; this complication may be preventable with close attention to catheter position and serum levels of potassium, magnesium, and calcium.

Respiratory failure connotes the lack of adequate gas exchange which, in the past, prompted aggressive attempts to normalize pH, partial pressure of carbon dioxide, and arterial oxygen tension. Such strategies employed the use of supraphysiologic tidal volumes, resulting in excessive distention injury to the lung. As highlighted in other chapters (► Chap. 11), not only can the lung architecture be damaged, but this can also perpetuate the systemic release of inflammatory mediators, thus adding further to the cascade underlying the process of MODS. In addition to reducing further lung injury by mechanical ventilation, special attention must be given to reduce the risk of ventilator-associated infection (VAI), which can occur in up to 5% of mechanically ventilated PICU patients.

The degree of fluid overload may carry prognostic significance; poor outcomes are associated with higher percentages of total body fluid overload.

Acute kidney injury frequently requires aggressive supportive measures. This begins with vigorous fluid administration. The fluid restriction that is often needed in a patient with established, intrinsic, oliguric/anuric renal disease to maintain euvolemia may not be warranted in the patient with multiple organ failure and ongoing capillary leak as maintenance of adequate circulating volume is essential. With the endothelial injury that these patients incur, they frequently develop total body fluid overload. As described above, there is

increasing evidence that the degree of fluid overload has important prognostic significance. When examining the use of CRRT in MODS patients with ≥3 organ failures, the percent fluid overload prior to initiation of CRRT is significantly higher among nonsurvivors than survivors, and it is independently associated with survival. When children with MODS were treated aggressively with CRRT, their survival rates compared favorably to historical controls. Early CRRT use is emphasized to mitigate the deleterious effects of volume overload and to allow for advancement of nutrition.

Endocrine issues may also play an important role in the care of patients with MODS. Early trials in adult surgical patients found that intensive insulin therapy (blood glucose concentrations maintained between 80 and 110 mg/dL) reduced mortality, bloodstream infections, the number of red blood cell transfusions, and the incidence of both renal failure and critical illness polyneuropathy. However, more recent studies have not confirmed these findings suggesting that tight glucose control may not influence outcomes, even in adult ICU patients. Hyperglycemia was identified as an independent correlate of mortality among patients receiving either mechanical ventilation or vasoactive infusions. Additionally, organ dysfunction (≥3 organs failed) is significantly associated with hyperglycemia. However, a multicenter randomized controlled trial in pediatric patients failed to demonstrate that tight glucose control had any impact on major clinical outcomes including days alive and ventilator-free days. Thyroxine infusions have been employed in a small series of patients with cardiogenic shock with improvements in cardiac index, pulmonary capillary wedge pressure, and mean arterial pressure. Further, the measurement of cortisol levels has been suggested as a means to guide the administration of hydrocortisone in the setting of shock. In sum, it is clear that further studies are necessary to best inform interventions aimed at altering the endocrine system in children with MODS.

Antimicrobials should be administered in a timely manner when a suspected or documented infection exists. Empiric coverage should be initiated as soon as possible with reproducible data suggesting that the timely initiation of antimicrobials is associated with improved outcomes among patients with sepsis. The timely initiation of antibiotics should be based on local protocols and should incorporate the institution's patterns of expected pathogens and resistant organisms, as well as the patient's known colonizing flora. Broad-spectrum antimicrobials should be tailored as soon as speciation and sensitivities are available to prevent the emergence of resistant pathogens. Strict handwashing by caregivers is essential in the prevention of hospital-acquired infection. Attention to sterile technique during intravascular catheter placement and care is of utmost importance. Furthermore, prompt removal of catheters prevents colonization and the continued breach of skin integrity, which should further decrease infectious risk.

Additionally, attention should be focused on the anticipation and correction of abnormal hematologic findings. The administration of packed red blood cells may improve oxygen delivery in anemic patients. Although not specific for MODS patients, a multicenter, randomized trial among PICU patients found no difference in outcome between threshold hemoglobin values of 9.5 g/dL and 7 g/dL. Platelets should be administered to bleeding patients with thrombocytopenia. Vitamin K and plasma should be used to attempt to correct clinically significant coagulation defects. The use of granulocyte macrophage colony-stimulating factor (Gm-CSF) in neonates with sepsis and neutropenia has been found to improve outcomes. Similarly, there are emerging data to suggest that the use of Gm-CSF in pediatric patients with sepsis may improve survival.

Nutritional support should be provided as early as possible in the care of critically ill patients. A lower risk of intestinal permeability defects and multiple organ failure have been demonstrated in patients fed enterally early (within 6 h of admission) compared to those fed late (>24 h after admission). Among enterally fed critically ill children receiving mechanical ventilation, energy repletion is independently associated with survival.

36.7 Specific Therapeutic Consideration in MODS

Specific therapeutic considerations in MODS are centered around specific pathobiologic phenotypes (Table 36.4). Thrombocytopenia-associated multiple organ failure is manifest by endothelial dysfunction, impaired ADAMTS13 activity, and production of von Willebrand factor ultralarge multimers. This results in a consumptive coagulopathy with microvascular and organ injury. Therapeutic plasma exchange may restore ADAMTS13 activity, and eculizumab may be considered in the setting of atypical hemolytic uremic syndrome.

Immunoparalysis-associated multiple organ failure may be associated with both decreased innate and adaptive immune function. Treatment is directed toward the underlying condition; however, Gm-CSF may prevent secondary infection. Reducing or discontinuing immunosuppressive agents may be indicated.

Critical pertussis-associated multiple organ failure is manifest by hyperleukocytosis and pulmonary hypertension. Margination of neutrophils and lymphocytes lead to endothelial injury and cellular plugging of pulmonary arterioles, resulting in cardiopulmonary collapse. Leukoreduction may be indicated along with the appropriate antimicrobials. Extracorporeal support may be useful in some cases.

Sequential multiple organ failure is characterized by lymphoproliferation in the setting of disrupted activation-induced cell death, leading to unchecked viremia. This is most commonly found in patients with Epstein-Barr virus, resulting in posttransplant lymphoproliferative disorder. The mainstay of therapy is the reduction of immunosuppressant agents or the use of an anti-CD20 monoclonal antibody (rituximab).

Table 36.4 Inflammatory phenotypes and adjunctive therapeutic modalities

Phenotype	Therapy
Thrombocytopenia-associated multiple organ failure	Plasmapheresis, eculizumab
Immunoparalysis-associated multiple organ failure	Gm-CSF, decreased immunosuppression
Hyperleukocytosis and pulmonary hypertension-associated multiple organ failure	Extracorporeal leukoreduction Appropriate antimicrobials
Sequential multiple organ failure with liver failure	Cessation of immunosuppression Rituximab
Macrophage activation syndrome	IVIG, anakinra, tocilizumab

Notes: *Gm-CSF* granulocyte macrophage colony-stimulating factor, *IVIG* intravenous immunoglobulin

Macrophage activation syndrome represents a hyper-inflammatory state characterized by endothelial disruption, macrophage production, disseminated intravascular coagulation, hepatobiliary dysfunction, and hyperferritinemia. Anti-cytokine therapy may be indicated in this phenotype with the IL-1 receptor antagonist (anakinra) or IL-6 blockade with tocilizumab. Hemophagocytic lymphohistiocytosis (HLH) is classified into primary and secondary forms. In primary (familial) HLH, inherited genetic mutations result in reduced cytotoxic T-cell and NK-cell function and/or other functional immunologic abnormalities. Secondary HLH results from both malignant and nonmalignant conditions, resulting in reduced function of these cells, excessive macrophage activation, and excessive cytokine production. Treatment may include steroids, plasma exchange, and intravenous immunoglobulin. Hematopoietic cell transplantation may be required for the treatment of primary HLH.

36.8 Summary

Multiple organ dysfunction syndrome (MODS) results from a variety of insults, most commonly sepsis and trauma. It often follows a common pathway once systemic inflammation cascades are triggered, and endothelial injury results in sequential organ dysfunction. Mortality remains high, roughly correlating with the number of organs involved, and survival is dependent upon treatment of the inciting process and optimizing supportive care. The validated PELOD score offers a reliable method of quantifying the severity of pediatric MODS. These critically ill infants and children are at risk for the development of progression of organ dysfunction and comorbid complications. Anticipation and prevention of these events with meticulous supportive care is currently the best available approach to improving outcomes. There are ongoing trials evaluating both targeted and nonspecific strategies to modulate the inflammatory process responsible for ongoing organ injury.

Review Questions

1. A 10-year-old male is admitted to the pediatric intensive care unit on postoperative Day 2 after undergoing exploratory laparotomy and drainage of abscesses secondary to a ruptured appendix. He develops altered mental status and hypotension. Vital signs are temperature 40 °C; heart rate 150 beats per minute, sinus rhythm; blood pressure 70/30 mmHg; respiratory rate 30 breaths per minute; and oxygen saturation 92% while receiving 15LPM of oxygen via a non-rebreather mask. Measurement of central venous pressure via a subclavian catheter is 1 mmHg. On examination, he is drowsy, but arousable, with nasal flaring and intercostal retractions. His abdomen is slightly distended with two closed-suction bulb drains draining serosanguinous fluid. His extremities are cool with a capillary refill of 3 s. After receiving 80 mL/kg of isotonic crystalloid solution, his blood pressure is 90/40 mmHg, the central venous pressure measurement is 4 mmHg, and he has had no urine output. He has become more somnolent and is beginning to grunt, while his oxygen saturation has dropped to 84% while on bilevel positive airway pressure of 20/10 cmH_2O.

   What is the next best intervention?

   A. Administer 40 mL/kg of 5% albumin.
   B. Administer 1 mg/kg intravenous furosemide.
   C. Begin an infusion of milrinone at 0.5 mcg/kg/min.
   D. Endotracheally intubate the child.
   E. Obtain computerized tomography of the head.

2. Which of the following scoring systems are used to quantify the severity of pediatric multiple organ dysfunction syndrome?
   A. Pediatric Risk of Mortality III (PRISM III)
   B. Injury Severity Score (ISS)
   C. Pediatric Index of Mortality-2 (PIM-2)
   D. Pediatric Logistic Organ Dysfunction (PELOD)
   E. Functional Status Scale

3. A 17-year-old female with a history of spina bifida and neurogenic bladder presents with a 2-day history of fever. In the emergency department, she is febrile to 39.4 °C, her heart rate is 140 beats per minute in sinus rhythm, blood pressure is 80/30 mmHg, respiratory rate is 30 breaths per minute, and oxygen saturation is 97% in room air. She has a clear sensorium, bounding pulses, and no organomegaly, and her skin is flushed with brisk capillary refill. There is a scant amount of urine in an indwelling catheter. A fluid bolus (20 mL/kg isotonic crystalloid) and antibiotics are administered, and she is admitted to the pediatric intensive care unit. *Which of the following statement is true regarding her care?*
   A. Acute kidney injury is the most likely explanation for her clinical condition.
   B. Additional crystalloid fluids should be administered prior to vasoactive infusions.
   C. Further fluid resuscitation should be restricted in order to prevent pulmonary edema.
   D. Parenteral nutrition is superior to enteral nutrition in this setting.
   E. The focus of infection is most likely pneumonia given her tachypnea.

4. Pathologic specimens of organs involved in MODS typically reveal infiltration with which of the following?
   A. Histiocytes
   B. Macrophages
   C. Monocytes
   D. Neutrophils
   E. Red blood cells

5. Anti-cytokine therapy using the IL-1 receptor antagonist (anakinra) has been suggested to be of benefit in treating this sepsis-induced MODS phenotype.
   A. Hyperleukocytosis and pulmonary hypertension-associated multiple organ failure
   B. Immunoparalysis-associated multiple organ failure
   C. Macrophage activation syndrome
   D. Sequential multiple organ failure with liver failure
   E. Thrombocytopenia-associated multiple organ failure

6. The use of granulocyte macrophage colony-stimulating factor (Gm-CSF) has been suggested to be of benefit in this MODS phenotype.
   A. Hyperleukocytosis and pulmonary hypertension-associated multiple organ failure
   B. Immunoparalysis-associated multiple organ failure
   C. Macrophage activation syndrome
   D. Sequential multiple organ failure with liver failure
   E. Thrombocytopenia-associated multiple organ failure

7. A 14-year-old male admitted to the pediatric intensive care unit with septic shock is somnolent but easily awakened. When prompted, he is following commands and conversing appropriately. His pupils are equal and reactive. He is receiving respiratory support via a CPAP mask set at 8 cmH_2O and 40% oxygen. He is found to have the following vital signs over the course of the 24-h period:
   Temperature: 36.7–40.1 °C
   Heart rate: 125–165 bpm
   Respiratory rate: 18–32 breaths per minute
   Mean arterial blood pressure: 50–68 mmHg
   His only laboratory results during that 24-h time period are as follows:
   Sodium: 132–139 mmol/L
   Potassium: 3.2–3.9 mmol/L
   Creatinine: 1.2–1.5 mg/dL (106–133 μmol/L)
   Lactate: 5.8 mmol/L
   WBC: 27,700 cells/μL
   Hemoglobin: 8.5 g/dL
   Platelet count: 105,000 cells/μL
   Aspartate transaminase: 75 U/L
   INR: 1.2–1.9
   pH: 7.33–7.39
   PaO_2: 65–93 mmHg
   $PaCO_2$: 31–43 mmHg
   Based on these values, his daily PELOD-2 score is which of the following?
   A. 1
   B. 3
   C. 6
   D. 7
   E. 10

Answers

1. D
2. D
3. B
4. D
5. C
6. B
7. D

Suggested Readings

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Healthcare-Associated Infections

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Contents

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Learning Objectives

- Describe the epidemiology of healthcare-associated infections (HAIs) in the pediatric intensive care unit (PICU).
- Describe potential sources of HAIs and risk-minimizing strategies.
- Describe the effect of HAIs on patient outcomes.
- Describe the identification, treatment, and outcomes of the following HAIs:
  - Bloodstream infections
  - Respiratory infections
  - Urinary tract infections
  - Infections in selected surgical patients
  - Infections in immunocompromised patients
- Understand the role of antibiotic stewardship when managing HAIs.
- Describe the general principles of infection control in the PICU.

37.1 Introduction

In 2004, The Joint Commission (TJC) adopted the reduction of HAIs as one of its specific safety goals. Minimal recommendations were for all hospitals: (1) to comply with the Centers for Disease Control and Prevention (CDC) hand hygiene guidelines and (2) to manage as "sentinel events" all identified cases of unanticipated death or major permanent loss of function associated with a HAI. Sentinel events are serious occurrences that suggest a significant underlying problem (usually in the system of care rather than due to an individual practitioner). A thorough analysis of the event and its underlying cause is to be conducted and remedies implemented to prevent a recurrence.

Since hospital accreditation by the TJC is essential for cost reimbursement by public payors, adherence to these standards and recommendations is a major goal for all hospitals in the United States.

A healthcare-associated, hospital-acquired, or nosocomial (from the Greek *nosokomos* = somebody who attends the sick) infection is a potentially avoidable complication that decreases overall patient safety. By elucidating the causes, employing successful preventive strategies and appropriate management of HAIs, risk reduction should occur and patients should be safer.

Recognition of the impact of HAIs on patient outcome has been long recognized. In the early nineteenth century, I.P. Semmelweis, an obstetrician and forefather of modern infection control, discovered that hands, air, and linen could spread infection. He noted higher mortality rates in mothers cared for by medical students, whose daily work included cadaveric dissection, as compared to midwife-attended mothers. Subsequently, he required that all providers attending to patients first wash their hands in a watery solution of chlorinated lime before providing care. This change reduced mortality from 18% to 2%. Similarly, in the 1890s, Joseph Lister's concept of surgical asepsis decreased post-amputation mortality from 45% to 15% by using handwashing, disinfectant-soaked dressings, and recognition of airborne contagion to wounds.

In 1946, the CDC was founded, evolving out of the Office of Malaria Control. The *Study on the Efficacy of Nosocomial Infection Control* supported by this group in the 1970s affirmed that comprehensive hospital infection control programs could prevent HAIs. In the 1980s, the CDC established the National Nosocomial Infections Surveillance (NNIS) System to provide a mechanism for reporting HAIs. This became the current National Healthcare Safety Network (NHSN) in 2005.

37.2 Epidemiology

Key definitions and data on pediatric HAIs in the United States are found in the National Healthcare Safety Network of the Center for Disease Control.

A healthcare-associated infection is defined by the NHSN as a "localized or systemic condition resulting from the presence of an infectious agent without evidence that the infection was present or incubating at the time of admission to the acute care setting."

A healthcare-associated infection is defined by the National Healthcare Safety Network (NHSN) as a "localized or systemic condition resulting from the presence of an infectious agent without evidence that the infection was present or incubating at the time of admission to the acute care setting." Practically, this has been defined as any new infection discovered after 48 h of admission to an acute care setting such as the PICU. HAI incidence data are consistently collected, reported, and available. The International Nosocomial Infection Control Consortium founded in 1998 collects data in developing countries. For developed nations, the World Health Organization (WHO) and, in Europe, the European Centre for Disease Prevention and Control collect and report data under the auspices of the European Union. In the United States, epidemiologic HAI data have been available from the NHSN of the CDC since 2005. This public healthcare surveillance system receives data from acute care facilities in the 50 states and Puerto Rico. The data are considered reliable because of the multi-institutional sources, the use of standardized definitions, and the consistent data collection processes. Moreover, participation and reporting are required for hospital reimbursement by the Center for Medicare and Medicaid Services (CMS).

Current reportable infections include urinary tract infections, surgical site infections, pneumonia, bloodstream infections, bone and joint infections, cardiovascular system infections, eyes-ears-nose-throat-mouth infections, gastrointestinal system infections, lower respiratory tract (non-pneumonia) infections, reproductive tract infections, skin and soft tissue infections, and disseminated infections. All of these infections have the potential to lead to sepsis, a major cause of morbidity and mortality in the PICU. Multinational data from 2015 (SPROUT Study) reveal that within PICUs, severe sepsis prevalence is 8.2% internationally and 7.7% in the United States. Mortality of this pediatric cohort was 25%. Mild to moderate disability was identified in one of five survivors. Although this study did not specifically assess hospital-acquired infections, at least some portion would represent hospital- or surgical-acquired sepsis.

The reported PICU incidence of HAIs is approximately 6%, or 14.1 infections per 1000 patient days. However, at any one time, between 9% and 14% of PICU patients have at least one nosocomial infection. Three infections account for 75% of all HAIs. As a group, they represent "device-related" infections: bloodstream, mostly central line-associated bloodstream infections (CLABSIs) (range, 28–41%), lower respiratory tract infections as a subset of a ventilator-associated condition/ventilator-associated complication (VAC) (range, 3–21%), and urinary tract infections associated with indwelling catheters (CAUTI) (range, 13–15%). However, the incidence per device days in US PICUs has begun to decrease over the last number of years as reported in a study of 64 PICUs between 2007 and 2012 (◘ Fig. 37.1). Incidence rates decreased from 4.7 to 1.0 per 1000 catheter days for CLABSI, 1.9 to 0.7 per 1000 ventilator days for infectious VACs, but remained about the same at 3.6 per 1000 catheter days for CAUTI. This same trend has been reported by the NHSN more recently (◘ Table 37.2) including a demonstrable decrease in CAUTIs. It is evident that CAUTIs are now the most common HAI in PICUs in the United States, similar to what is reported in adult ICUs. A much higher occurrence of PICU HAI by device days has been described in ICUs located in countries of lower socioeconomic status as reported by the International Nosocomial Infection Control Consortium: 7.9 per 1000 ventilator days for ventilator-associated infections, 6.1 per 1000 catheter days for CLABSI, and 5.6 per 1000

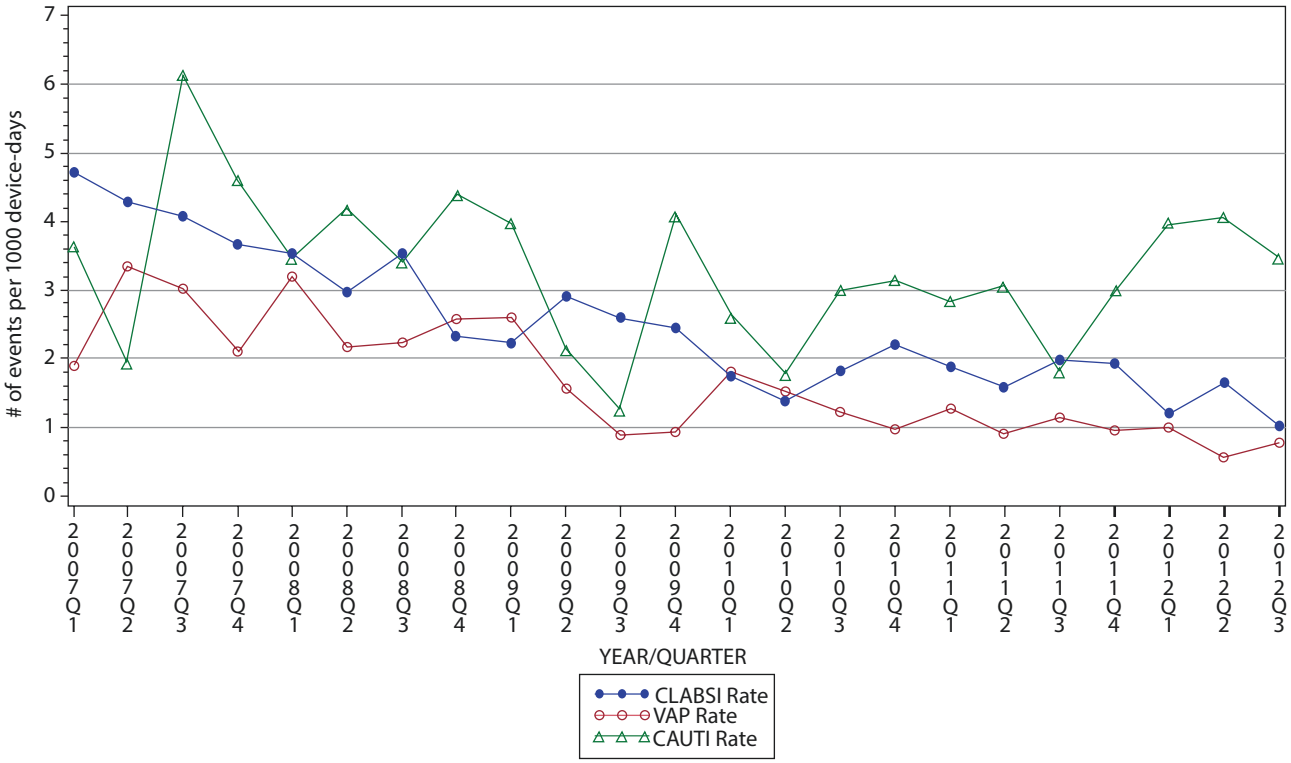

Fig. 37.1 Rates of CLABSI, VAP, and CAUTI in PICUs, January 2007 to September 2012. CLABSI: 888 events; 919,200 patient days; 403,307 line days. VAP: 261 events; 825,868 patient days; 174,509 ventilator days. CAUTI: 352 events; 879,409 patient days; 109,835 catheter days. *CLABSI* central line-associated bloodstream infection, VAP ventilator-associated pneumonia, CAUTI catheter-associated urinary tract infection, PICU pediatric intensive care unit. (Reproduced with permission from *Pediatrics*, Vol. 134, Page 709, Copyright 2014 by the AAP)

urinary catheter days. It is not clear why there is this difference, but contributing factors likely include limited resources, difficulty in surveillance, no mandatory standardization of infection control practices, and possible diagnostic difficulties.

A variety of pathogens (88% bacteria, 7% fungi, and 5% viruses) are associated with HAIs. Pathogen type and species vary by age and other patient factors. Table 37.1 is 2012 data from the European Centre for Disease Prevention and Control comparing micro-organisms identified in HAI by age group.

Improved device stewardship and "bundled" device care has reduced three PICU healthcare-associated infections: CLABSI, infectious VAC, and CAUTI.

The incidence of device-related HAIs has declined in the last decade attributable to a wider adoption of device-free care, early device removal, and a "bundled" approach to device maintenance. NHSN now reports a decrease in all three of the major device- related HAI as demonstrated in Table 37.2.

37.3 Risk Factors

Critically ill children have a higher risk of HAIs than other hospitalized patients. Disturbances in physiology and immunology allow infectious agents to flourish and necessitate indwelling devices that bypass natural dermatologic, mucosal, and respiratory barriers. Age, in addition to the primary disease process, contributes to a variable immunocompromised status in the PICU. Consequently, infants aged 2 months to 1 year have the highest incidence of HAI (39%) compared to other age groups. Nutritional, cardiopulmonary, and metabolic abnormalities further compromise children's ability to mount an effective host

Table 37.1 Pediatric microorganism prevalence in HAI by age group

Microorganism	Age group					
	All	<1 month	1–11 months	1–4 years	5–10 years	≥11 years
Coagulase-negative staphylococci	82 (21.0%)	33 (31.4%)	38 (21.3%)	3 (7.0%)	1 (3.1%)	7 (21.9%)
Staphylococcus aureus	41 (10.5%)	15 (14.3%)	14 (7.9%)	4 (9.3%)	4 (12.5%)	4 (12.5%)
Escherichia coli	37 (9.5%)	7 (6.7%)	17 (9.6%)	4 (9.3%)	4 (12.5%)	5 (15.6%)
Klebsiella spp.	37 (9.5%)	6 (5.7%)	21 (11.8%)	7 (16.3%)	2 (6.3%)	1 (3.1%)
Enterobacter spp.	27 (6.9%)	14 (13.3%)	10 (5.6%)	2 (4.7%)	0 (0.0%)	1 (3.1%)
Pseudomonas aeruginosa	26 (6.7%)	3 (2.9%)	10 (5.6%)	7 (16.3%)	4 (12.5%)	2 (6.3%)
Candida spp.[a]	23 (5.9%)	3 (2.9%)	12 (6.7%)	3 (7.0%)	1 (3.1%)	4 (12.5%)
Viruses	21 (5.4%)	3 (2.9%)	13 (7.3%)	4 (9.3%)	1 (3.1%)	0 (0.0%)
Enterococcus spp.	20 (5.1%)	5 (4.8%)	12 (6.7%)	2 (4.7%)	1 (3.1%)	0 (0.0%)
Streptococcus spp	18 (4.6%)	6 (5.7%)	5 (2.8%)	1 (2.3%)	4 (12.5%)	2 (6.3%)
Stenotrophomonas malthophilia[a]	12 (3.1%)	0 (0.0%)	8 (4.5%)	1 (2.3%)	3 (9.4%)	0 (0.0%)
Serratia marcescens	8 (2.1%)	4 (3.8%)	3 (1.7%)	1 (2.3%)	0 (0.0%)	0 (0.0%)
Acinetobacter baumannii	7 (1.8%)	3 (2.9%)	4 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clostridium difficile	4 (1.0%)	0 (0.0%)	1 (0.6%)	1 (2.3%)	2 (6.3%)	0 (0.0%)
Haemophilus influenzae	4 (1.0%)	0 (0.0%)	1 (0.6%)	1 (2.3%)	1 (3.1%)	1 (3.1%)
Moraxella catarrhalis	4 (1.0%)	0 (0.0%)	2 (1.1%)	1 (2.3%)	1 (3.1%)	0 (0.0%)
Proteus mirabilis	4 (1.0%)	0 (0.0%)	1 (0.6%)	1 (2.3%)	1 (3.1%)	1 (3.1%)
Aspergillus fumigatus	3 (0.8%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Other	12 (3.1%)	3 (2.9%)	4 (2.2%)	0 (0.0%)	2 (6.3%)	3 (9.4%)
Total	**390 (100.0%)**	**105 (100.0%)**	**178 (100.0%)**	**43 (100.0%)**	**32 (100.0%)**	**32 (100.0%)**

Source: Zingg et al. *The Lancet* (2017)
ECDC European Centre for Disease Prevention and Control, *HAI* Healthcare-Associated Infection
[a]Missing data about age for one isolate

Table 37.2 Comparative incidence of device-related infection

Condition	2003[a]	2015[a]
Central line-associated bloodstream infection	7.3	1–1.4
Ventilator-associated respiratory infection	2.9	0.6–0.8
Catheter-associated urinary tract infection	4.7	1.2–2.4

Source: CDC Annual Incidence Report
[a]Per 1000 device days

response. High rates of antibiotic exposure complicate treatment via emerging resistance and the selection of typically nonpathogenic organisms (e.g., fungi, *Propionibacterium acnes*). Many pharmacologic agents also interfere with immunologic processes. For example, histamine-blocking agents augment gastric and upper pharyngoesophageal flora, reducing bactericidal conditions associated with gastric acidity; corticosteroids alter macrophage and T-cell function; total parenteral nutrition (TPN) exposure, particularly before PICU Day 8, is associated with higher rates of HAI.

In addition, healthcare workers expose patients to pathogens, either their own or those carried from other patients. Staff frequently, although inadvertently, transmit infectious agents via their hands, equipment, and their respiratory and/or gastrointestinal tracts. Equipment surface testing often demonstrates contamination and demonstrates that these devices can serve as a reservoir for multidrug-resistant organisms (MDROs) such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and *Clostridium difficile*. Carpets, mattresses, beds, stethoscopes, thermometers, intra-aortic balloon pumps, humidifiers, nebulizers, pressure transducers, and enteral feeds have all been reported as sources of HAI outbreaks. Transmission of MDROs from contaminated devices or surfaces to patients occurs via direct contact with equipment, indirectly via the hands/gloves of staff, and less commonly via aerosols, water, or food. Fomite reduction strategies such as scrub policy, patient-dedicated equipment, routine chlorhexidine decontamination of surfaces, and routine patient decontamination attempt to mitigate this environmental risk.

37.4 Bloodstream Infection

Central line-associated bloodstream infection (CLABSI) contributes significantly to the cost and length of hospitalization and results in patient deaths. Approximately 90% of bloodstream infections are considered to be a direct complication of intravascular catheters. However, the NHSN definition, the one used in most epidemiologic studies, also includes as a CLABSI whenever an infectious organism (bacteria or fungus) is isolated from the blood in patients with intravascular catheters when no other source for the infection can be found. Thus, it is clinically challenging to separate bloodstream infections *caused* by an intravascular catheter from those that have *no relationship* to the catheter. For example, patients with frequent gut translocation will demonstrate transient bacteremia or fungemia resulting in line contamination. The catheter is not the cause of the infection; it only demonstrates the susceptibility

of indwelling devices to organism adherence and colonization from any source. There is no clinical means to clearly attribute positive central line cultures to a translocation process rather than to an outside environmental cause or a caregiver's line contamination.

Most bloodstream infections in the pediatric intensive care unit are a direct complication of intravascular catheters.

The International Forum on Sepsis in Infants and Children has proposed pediatric definitions for diagnosing central venous catheter-related infections that are slightly modified from the NHSN definitions (Table 37.3). They are designed to standardize pediatric-focused definitions, guide treatment, and provide consistency in research.

If one suspects a catheter-related infection, it is best to obtain both a central line blood culture and one obtained via a fresh peripheral venipuncture simultaneously prior to antibiotic administration.

The decrement in accurate pediatric CLABSI diagnosis is, in part, caused by lower sensitivity of pediatric blood cultures due to the small volumes obtained, the lack of routine catheter tip cultures, and the initiation of antibiotics before confirmation of infection. Within the SPROUT cohort of children with severe sepsis, only 25% had positive blood cultures although 65% of patients had organisms isolated. The ideal practice, if CLABSI is suspected, requires two blood cultures: one through the intravascular device and one fresh venipuncture culture prior to antibiotic administration. A colony count from blood drawn through the catheter that is five- to tenfold greater than the peripheral colony count OR a central line culture that is ≥100 CFU/mL alone is suggestive of a line-related infection. Data obtained in pediatric oncology patients via continuous blood culture monitoring suggests that if the central line blood culture is positive ≥2 h *before* the peripheral culture, CLABSI is likely.

Given that femoral catheters are used most commonly for access in the PICU, they are also the most common source of CLABSI, followed by internal jugular and then subclavian catheters (e.g., subclavian catheters are the least used). However, there appears to be no difference in the rate of infections by catheter site in children. These lines are either non-tunneled, short-term catheters or tunneled, long-term catheters. PICCs (*p*eripherally *i*nserted *c*entral *c*atheters) are placed by threading the catheter tip from a superficial, peripheral entry point in the upper or lower extremity, or even the scalp, to a central venous location using a guidewire. These lines can stay in place for an intermediate length of time, sometimes even as long as 6 months to a year if carefully maintained. Until recently, CLABSI rates associated with PICC lines were considered lower (0.2–1.4 per 1000 catheter days) than those associated with percutaneous tunneled or non-tunneled catheters in some studies, perhaps justifying PICC's higher overall expense. However, a 2018 study reported a threefold higher rate of PICC-related CLABSI and higher thromboembolic complications, suggesting caution also with PICC lines.

Hemodialysis catheters are 4 times more likely to become infected than standard central venous catheters.

Arterial and dialysis catheters have also been studied in PICU patients. Hemodialysis catheters are associated with fourfold higher CLABSI risk in children than other central venous lines. This is similar to adult populations. In contrast, the risk of an arterial catheter-related infection in the PICU is extremely low (<0.6%). However, the incidence of an arterial line infection is a bit higher in adult populations. Adults who have arterial catheters for 2 days or more are 2–6 times more likely to develop a bloodstream infection. The risk of infection is mitigated by avoiding backflow of blood into the pressure tubing.

Coagulase-negative staphylococci are the most common cause of catheter-related infections in the pediatric ICU.

Gram-positive organisms are the most common bacteria responsible for pediatric CLABSI. Coagulase-negative staphylococci are most common (37%) followed by *Staphylococcus aureus* (13%) and *Enterococcus* species (13%). Gram-negative bacilli, including *Enterobacter* species, *Escherichia coli*, *Pseudomonas* species, and *Klebsiella* species, account for 14–25% of infections. Fungi, mainly *Candida* species, are isolated up to 13% of the time, particularly from patients with severe infection.

Table 37.3 Definitions of catheter-related bloodstream infection

Definite catheter-related BSI	*One of the following PLUS at least one peripheral positive blood culture with the same organism*
	Blood culture positive with >5:1 ratio of CFU/mL central line vs. peripheral
	Central line culture is positive ≥2 h earlier than peripheral
	Catheter tip ≥15 CFU/catheter segment if semiquantitative; ≥1000 CFU/catheter segment if quantitative
	Positive culture from pus at catheter exit site
Probable catheter-related BSI	*Either one of the following*
	Clinical sepsis PLUS positive catheter tip/segment culture. Patient improves within 48 h of catheter removal WITHOUT antibiotics
	Clinical sepsis with ≥2 blood cultures, including one peripheral, positive for common skin organism[a] in the absence of catheter segment culture and no other sources
Possible catheter-related BSI	*Either one of the following*
	Clinical sepsis PLUS positive catheter tip/segment culture. Patient improves within 48 h of catheter removal WITH antibiotics
	Clinical signs of infection PLUS *one* positive blood culture (either from central line or peripheral) with a common skin organism[a] in absence of catheter segment culture and no other apparent sources of infection

Source: Adapted from Randolph et al. (2005)
CFU colony-forming units, *BSI* Bloodstream infection
[a]Skin organisms, e.g., *Bacillus* species, coagulase-negative staphylococci, diphtheroids

In PICU patients, femoral catheters do not pose a higher risk of infection than central catheters placed elsewhere.

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CLABSI pathogenesis is multifactorial. Migration of skin flora from the insertion site to the catheter tip generally occurs first, followed by irreversible attachment of the flora to the *extra*luminal catheter surface in a biofilm. This occurs within 10 days of catheter placement. After 10 device days, *intra*luminal colonization in a biofilm is more common. Biofilm is a proteinaceous matrix that aids strong organism adherence to foreign material and reduces penetrance of antibiotics. Since migration of skin flora is an important means of contamination, catheter placement in areas with dense skin flora would seem to predict risk. Additionally, the number of catheter lumens might also be expected to increase risk. Although these factors contribute to adult CLABSI, this does not appear to be the case for children based on minimal available data. Adult CLABSIs occur least commonly for subclavian and most commonly for internal jugular vein catheters. Femoral lines are generally avoided in adults since femoral catheters have higher bacterial *colonization rates* (but not infection). Children have neither a higher colonization nor a higher infection rate of femoral vein catheters. It is unclear how closely catheter colonization is related to developing infection. There is some pediatric data indicating that only 8% of colonized catheters result in bacteremia.

Bacteria, especially staphylococci, adhere to blood proteins in microthrombi along catheter surfaces. Thus, the elimination of microthrombi on catheters via heparin-bonded catheters, heparin locks or flushes, and as needed tPA instillation might mitigate CLABSI risk.

Catheter material is also likely related to colonization, since there is higher bacterial adherence to polyvinyl chloride and polyethylene catheters and less adherence to polyurethane, silicone, or Teflon catheters. Organism characteristics also contribute to CLABSI pathogenesis. For example, coagulase-negative staphylococci adhere to catheter polymer surfaces better than *Escherichia coli* and *Staphylococcus aureus*, often secreting protective substances that make

Table 37.4 Risk factors for catheter-related bloodstream infections

Increased risk	Decreased risk	No change in risk
Catheter material (polyvinyl chloride, polyethylene) Compromised sterility during insertion Younger age Number of catheter days (>5) Frequent line entry/cap changes TPN infusion Poor mucosal and skin integrity Immunocompromised state Microthrombi Catheter use for dialysis/pheresis	Catheter material (polyurethane, silicone, Teflon) Adherence to insertion and maintenance bundles Older age Reduced catheter days (<5) Lower line entry/cap changes Enteral nutrition Intact skin Heparin-bonded catheters	Catheter location Number of catheter lumens (minimal data)

TPN total parenteral nutrition

them less susceptible to host defenses. *Staphylococcus aureus* adheres to host proteins that cover catheters. Thrombogenic catheters (PICCs, catheters in hypernatremic patients or those suffering trauma) increase the risk of infection as bacteria adhere to clot proteins. The elimination of microthrombi on catheters via heparin-bonded catheters, heparin locks or flushes, and as needed recombinant tissue plasminogen activator (tPA) instillation might mitigate CLABSI risk. Other risk factors that influence CLABSI include TPN, length of insertion time >5 days, and incomplete sterility during insertion. A summary of CLABSI-related risk factors is listed in Table 37.4.

Attention to catheter type, number of catheters used, catheter days, sterility during insertion, and catheter maintenance all reduce infection. The most important factor is limiting the number of catheter days; this includes avoiding central line placement when possible and early removal once need for central access (e.g., central venous pressure measurement, infusion of high-risk medications, TPN) has ceased.

37.4.1 Prevention

A working group representing the Society of Critical Care Medicine, the American Academy of Pediatrics, and the Healthcare Infection Control Practices Advisory Committee of the CDC has developed recommendations for pediatric CLABSI prevention. Based on these recommendations and recent literature, Table 37.5 depicts general recommendations for infection prevention in central venous catheters, PICCs, hemodialysis catheters, and pulmonary artery catheters.

Since it is not feasible to determine which of these individual recommendations is most effective, a "bundle" approach has been recommended. "Vascular bundle" interventions have been divided into two subgroups – the insertion bundle, governing interventions to insure maximum sterility at the time of placement, and the maintenance bundle, designed to maximize sterility during the life of the line (▶ Box 37.1).

Table 37.5 Interventions to prevent pediatric catheter-related infections

Hand hygiene	Proper handwashing with conventional antiseptic containing soap/water or waterless, alcohol-based gels or foams *before* palpation of the site, insertion of the catheter, accessing, manipulation, or dressing the site
Catheter selection	Use the catheter with the minimal number of lumens required for management
	No recommendation for the use of antibiotic impregnated catheters, although data suggest they are useful in adults
	Use cuffed hemodialysis catheter if to be used for over 3 weeks
	Heparin-bonded catheters are preferred since they decrease the incidence of catheter-related infections
Catheter site	No preference in pediatric patients although in older patients, a subclavian site is associated with the lowest rate of infection
	Clean site with 2% chlorhexidine preparation[a] (best for patients ≥2 months old), povidone iodine, or 70% alcohol. Let dry before starting insertion
Catheter insertion	Use maximal barrier techniques during insertion including sterile gloves, cap, mask, gown, and a large sterile sheet
Catheter care	Do not use topical antibiotic ointment (except for hemodialysis catheters)
	Do not use chlorhexidine sponge dressings in neonates <7 days or gestational age < 26 weeks
	Use sterile gauze/tape or sterile, transparent, semipermeable dressing
	Change dressing when soiled, damp, or bloody
	Change dressings every 2 days for gauze dressings, every 7 days for transparent dressings. Use 2% chlorhexidine (≥2 months), although povidone iodine or 70% alcohol is acceptable
	Designate one port for TPN/intralipids exclusively. Complete infusion within 24 h
	Do not use in-line filters to reduce infection
	Do not use antibiotic lock prophylactically
	Change IV administration sets Q72 h if only crystalloid/dextrose/amino acids; if blood administration/lipid administration, change every 24 h; change caps Q72 h
Catheter changes	Do not change catheters routinely, including for unidentified source of fever
	Do not change catheter routinely for bacteremia/fungemia if source unlikely to be the catheter
	Replace short-term central catheter if purulence at insertion site
	Replace central catheter if patient is unstable hemodynamically and suspect catheter-related infection
	Do not replace catheter by rewiring; if suspect catheter-related infection, place new catheter in a different site

[a]Chlorhexidine 2% is the preferred preparation and maintenance agent
IV intravenous; *TPN* total parenteral nutrition

Box 37.1 Central line catheter-care bundles

Insertion bundle

- Wash hands before the procedure
- For all children aged ≥2 months, use chlorhexidine gluconate to scrub the insertion site for 30 s for all areas except the groin, which should be scrubbed for 2 min. Scrubbing should be followed by 30–60 s of air-drying
- No iodine skin prep or ointment is used at the insertion site
- Prepackage or fill the insertion cart, tray, or box including full sterile barriers
- Create an insertion checklist, which empowers staff to stop a non-emergent procedure if it does not follow sterile insertion practice
- Use only polyurethane or Teflon catheters
- Conduct insertion training for all care providers, including slides and video

Maintenance bundle

- Assess daily whether catheter is needed
- Catheter-site care
  - No iodine ointment
  - Use a chlorhexidine gluconate scrub at sites for dressing changes (30-s scrub, 30-s air-dry)
  - Change gauze dressings every 2 days unless they are soiled, dampened, or loosened
  - Change clear dressings every 7 days unless they are soiled, dampened, or loosened
  - Use a prepackaged dressing-change kit or supply area
- Catheter hub, cap, and tubing care
  - Replace administration sets, including add-on devices, no more frequently than every 72 h unless they are soiled or suspected to be infected
  - Replace tubing that is used to administer blood, blood products, or lipids within 24 h of initiating infusion
  - Change caps no more often than 72 h (or according to manufacturer recommendations); however, caps should be replaced when the administration set is changed
  - The prepackaged cap-change kit or supply area elements to be designated by the local institution

[a]According to the CDC recommendations. Source: Adapted from Miller et al. (2010)

A study of 29 NACHRI-affiliated PICUs using both insertion and maintenance bundles demonstrated a 43% reduction in CLABSIs associated with compliant bundle practice. Comparative modeling found that the pediatric maintenance bundle alone predicted a decrease in infection. This was in contrast to adult studies where optimizing compliance with the insertion bundle was the main effector. Another meta-analysis of adult, pediatric, and neonatal studies evaluating bundled catheter care revealed consistent and significant risk reduction (56%) in the CLABSI incidence with results persisting at 6-month reevaluation; among PICUs in that report, there was a 42% risk reduction. Two NICUs and one PICU reported cost savings related to CLABSI prevention (CLABSIs cost hospital systems $43,000 per patient on average). In an analysis of the bundle elements, the use of hand hygiene, having support of opinion leaders, central line kits, appropriate selection of venous access site, nurse empowerment to stop procedures when contamination occurred, and minimizing line access were all significant risk mitigators for pediatric CLABSI.

Recommendations for insertion and maintenance bundles for arterial catheters are different. Insertion with sterile gloves after careful handwashing and the site preparation with disinfectants is considered appropriate and sufficient. Full sterile dress and site protection is generally not necessary. Disposable transducer assemblies should be used and replaced every 96 h. Closed flush systems are optimal, if safe and feasible. If dealing with small volumes, a syringe/stopcock should be used with careful attention to cleanliness with manipulation. If the system is accessed through a diaphragm, the diaphragm should be cleaned with an antiseptic solution first. Given the very low incidence of infection, routine changing of arterial catheters is not recommended.

37.4.2 Treatment

In the event of a Gram-negative or fungal-infected catheter, clearance of the infection is often delayed, and outcomes are worse if the catheter is not removed.

Difficulty placing and maintaining intravascular devices in infants and children can affect decisions about the management of a line-related infection. Other factors affecting treatment are the type of organism discovered, the relative risk of new line placement, and patient stability. CLABSI treatment without line replacement is more often successful for Gram-positive organisms. In uncomplicated Gram-positive infection, appropriate systemic antibiotics should be given for 10–14 days. In coagulase-negative staphylococcal infection, where the line is removed, 5–7 days are likely sufficient. With fungal and Gram-negative infections, clearance without line removal is less likely to be successful and can contribute to patient risk. Treatment duration of 7–10 days after line removal for Gram-negative cases and 14 days for patients with fungemia is appropriate. In a retrospective review of infants with Gram-negative and fungal CLABSI, patients wherein lines were retained after CLABSI diagnosis experienced significantly longer antibiotic usage (17 versus 13 days) and more frequent sequential positive blood cultures (47% versus 22%). Infants with Gram-negative bacteremia in this cohort demonstrated higher mortality when catheters were retained: 43% versus 7%. At least 14 days of antifungal therapy from the last date of a positive culture should be given if infection occurred in a tunneled catheter.

37.5 Respiratory Infection

The epidemiology of healthcare-associated respiratory infections, particularly viral infections, is not well established despite its common occurrence in the PICU. Three to 19 percent of PICU patients experience healthcare-associated respiratory infections with a subset of these patients experiencing *ventilator-associated* infections from any pathogen (virus, bacteria, or fungus). Healthcare-associated viral respiratory infections (HA-VRI) were present in 702 PICU patients out of a multicenter cohort of 3600 patients, an incidence of 2.8 HA-VRI per 1000 PICU days. Ventilator-associated respiratory infections are divided into two groups: early and late onset. The former develops within 4 days of PICU admission usually with *Moraxella catarrhalis*, *Haemophilus influenzae*, and/or *Streptococcus pneumoniae*. Late infections are associated with more traditional hospital-associated organisms such as Gram-negative bacilli most commonly *Escherichia coli* and *Pseudomonas aeruginosa* as well as *Staphylococcus aureus*, especially methicillin-resistant species.

Lack of definitional clarity, inconsistent applications across institutions, and the published literature contribute to variable incidence and prevalence reporting. This variability clouds characterization of patient outcome. This is particularly true for epidemiologic data of device-associated pneumonia. The

decades-old definition of ventilator-associated pneumonia (VAP) established by the NHSN is based on clinical, radiographic, and microbiologic data in those intubated for >48 h. To be considered a VAP, there must be:

1. Radiologic evidence of pneumonia on chest radiograph
2. A clinical exam suggesting pneumonia, including abnormal temperature, abnormal lung exam/increased work of breathing, abnormal secretions
3. Evidence of worsening gas exchange

This definition was designed with hopes that combining multiple forms of clinical data would improve specificity. However, the VAP definition has criteria that are open to subjective interpretation (Table 37.6). Even respiratory cultures must be carefully interpreted since endotracheal cultures may be contaminated by upper airway secretions or simply indicate colonization, resulting in high sensitivity but rather low specificity. Criteria have been proposed to guide the interpretation of microbiology data in the setting of suspected respiratory infection (Table 37.7).

NHSN clinical definitions for VAP have not correlated well with autopsy findings (the gold standard) in pediatric patients. Applying these definitions, the pediatric VAP incidence was reported to be 3–13 per 1000 ventilator days in earlier PICU publications. However, CDC annual data demonstrate a reduced VAP incidence nationally from 1.6 per 1000 ventilator days in 2007 to 0.6 per 1000 ventilator days in 2012. It is unclear whether this represents improvements in care, increase in management of respiratory failure with noninvasive means, "bundled" interventions, or variability in VAP identification due to subjectivity in the definition.

It is unreliable to diagnose VAP solely by an endotracheal aspirate culture or changes on a chest radiograph. Instead, a specific increase in oxygenation or ventilator requirements should be present, and respiratory secretion data (culture, appearance, location) consistent with infection are necessary. White blood cell counts and temperature elevation/depression may also be useful if there is a change from baseline. Chest radiographs should be interpreted cautiously since findings may appear to be infectious, but actually are not.

Table 37.6 Clinical definitions of healthcare-associated pneumonia

Healthcare- associated pneumonia	Developing ≥3 days into hospitalization or < 7 days from discharge	
Ventilator-associated pneumonia	Developing ≥48 h after initiation of mechanical ventilation with radiographic evidence of pneumonia[a]	
	Child ≤ 1 year	*Child > 1 and <12 years*
	Radiographic evidence of pneumonia[a]	*Radiographic evidence of pneumonia*
	PLUS *Worsening gas exchange*[b]	*PLUS* *Worsening gas exchange*
	PLUS *≥3 of the following* Cough Wheezing, rales, or rhonchi Apnea, tachypnea, nasal flaring with retraction of the chest wall, or grunting New or increased lower respiratory tract secretions, change in character of secretions, or increase in suctioning requirements Temperature instability Bradycardia or tachycardia for age	*PLUS* *≥3 of the following* Cough Wheezing, rales, or rhonchi Apnea, tachypnea, nasal flaring with retraction of the chest wall, or grunting New purulent sputum or change in character of sputum, increased respiratory secretions, or increased suctioning requirements Temperature > 38.4 °C or < 36.5 °C with no other recognized causes Peripheral WBC >15,000 with >10% bands or WBC < 4000

Source: Adapted from Langley and Bradley (2005)
WBC white blood cell count
[a]New or progressive infiltrate, either bronchoalveolar or interstitial, cavitation, abscess, or pneumatocele
[b]Increase in oxygenation desaturation episodes, increased oxygen requirement, or increased ventilation requirement

Table 37.7 Microbiologic criteria for confirmation of "definite" pneumonia

Deep expectoration sputum	Sample examined (10–20 oil fields)
	+ microorganisms AND > 25 neutrophils AND < 10 squamous epithelial cells/field at ×100 magnification
Sputum obtained in ventilated patients	Endotracheal aspiration $\geq 10^5$ CFU/mL
	Bronchoscopy with BAL $\geq 10^4$ CFU/mL
	Bronchoscopy with PSB $\geq 10^3$ CFU/mL
	Blind PSB $\geq 10^3$ CFU/mL
Other microbiologic detection	Positive blood culture for respiratory tract pathogen
	Positive pleural fluid culture
	Virus/viral antigen detection in respiratory secretions
	Diagnostic single-AB titer (IgM) or fourfold increase in paired sera IgG
	Histopathologic evidence of pneumonia
	+ PCR/genomic ID of respiratory pathogens in the lower respiratory tract

Source: Adapted from Langley and Bradley (2005)
BAL bronchoalveolar lavage, *PSB* protected specimen brush, *AB* antibody, *CFU* colony-forming units, *PCR* polymerase chain reaction, *ID* identification

Another contributor to reduced VAP reporting may be what has been recently called ventilator-associated tracheitis (VAT). A positive tracheal aspirate with purulence may represent tracheitis or tracheobronchitis rather than colonization or a contaminated sample, especially in patients with minimal fever, no findings consistent with pneumonia on chest radiograph, and no changes in oxygenation/ventilation. Tracheobronchitis has been found to be the second most common cause of healthcare-associated infections in adult ICUs.

One recent pediatric study (2016) defined VAT as an infectious ventilator-associated condition wherein there are:

1. Absent radiographic evidence of lower respiratory infection
2. Hyper- or hypothermia (>38 °C or <36 °C)
3. An abnormal leukocyte count by age (≥15,000 or <4000 leukocytes/μL for children ≤12 years; ≥12,000 or <4000 leukocytes/μL if child >12 years)
4. Purulent respiratory secretions (moderate or higher WBC count on Gram stain)
5. A single organism positive respiratory culture at >10,000 CFU/mL (or semiquantitative equivalent)

In that study and using that definition, the VAT incidence was 7.3% (5.19 per 1000 ventilator days). The diagnosis of VAT in that report predicted longer length of stay and more ventilator days, but not increased mortality.

Some posit that improved accuracy in skilled point-of-care ultrasound may enhance the diagnosis of VAP and aid distinction from VAT.

In 2013, the CDC adopted new definitions for VAP for adults, now called ventilator-associated events or complications (VAC). Definitions were expanded to include both infectious and noninfectious VAC. This schema reduces subjectivity in diagnostic criteria in order to improve definitional specificity and sensitivity. The literature suggests that patients with VACs suffer increased ventilator days, ICU length of stay, and mortality. VAC criteria are illustrated in ◘ Table 37.8. Important differences in previous VAP criteria and the VAC schema are:

(a) Broadening of the definition to include noninfectious ventilator-associated complications
(b) Events defined by an objective increase in oxygen and/or positive end-expiratory pressure (PEEP) requirement ($FiO_2 \geq 0.2$ and/or PEEP by ≥ 3 cm H_2O)
(c) Eliminating radiographic data
(d) Defining subcategories:
    1. *Infection-related ventilator-associated complication (IVAC)* defined by length of antibiotic exposure and either abnormal temperature or WBC count
        (i) *Possible ventilator-associated pneumonia (PVAP)* – purulent secretions OR positive culture OR other positive test as described in the three criterion in ◘ Table 37.8

Efforts have been made to test and adapt these adult definitions to ventilated pediatric patients with focus on specific and sensitive changes in oxygenation, ventilation, temperature, and biochemical markers in children. These investigators are assessing suitability of other factors such as microbiological data and cultures to define subcategories. Pediatric adaptations to VAC criteria as compared to adult VAC are displayed in ◘ Table 37.9. Notable differences in pediatric working definitions are (1) using an FiO_2 change of 0.25 (rather than 0.20), (2) using an increase in *MAP (mean airway pressure*) by 4 cm H_2O (vs. 3 cm H_2O *PEEP*), (3) eliminating temperature and WBC from diagnostic criteria, (4) not requiring a positive culture or positive secretions for diagnosis of AVAC – antimicrobial-related ventilator-associated condition (the author's preferred terminology) – and (5) removal of radiographic criteria, hence combining tracheitis and tracheobronchitis with lower respiratory tract infections.

Four multicenter studies using modified pediatric criteria as well as the VAC criteria of the CDC found a low sensitivity (56–66%) but a very high specificity (100%) when applying this algorithm in the PICU. An additional study evaluating pediatric VAC criteria in 47 PICUs in the United States, Canada, and Australia found that strict application of VAC criteria would result in a significant "reduction" in the identification of ventilator-associated infections by PICU attendings in their routine clinical practice. Attending physicians diagnosed 89 of 229 patients with a ventilator-associated infection clinically, whereas strict, retrospective, application of the CDC VAC criteria identified only 5 of these 89 patients with a ventilator-associated infection. This difference highlights the difficulties of diagnostic criteria for pediatric VAC. Are PICU physicians "overcalling" infection, needlessly exposing patients to antibiotics for what are noninfectious declines in patient respiratory status? Or do the formal criteria have poor sensitivity for pediatric ventilator-associated infections, potentially delaying treatment and leading to worse outcomes?

Table 37.8 CDC ventilator-associated events algorithm

Patient has a baseline period of stability of improvement on the ventilator, defined by ≥ 2 calendar days of stable or decreasing daily minimum* FiO_2 or PEEP values. The baseline period is defined as the 2 calendar days immediately preceding the first day of increased daily minimum PEEP or FiO_2

*Daily minimum defined by lowest value of FiO_2 or PEEP during a calendar day that is maintained for > 1 hour.

After a period of stability or improvement on the ventilator, the patient has at least one of the following indicators of worsening oxygenation:

1) Increase in daily minimum*FiO_2 of ≥ 0.20 (20 points) over the daily minimum FiO_2 of the first day in the baseline period, sustained for ≥ 2 Calendar days.
2) Increase in daily minimum* PEEP values of ≥ 3 cmH2O over the daily minimum PEEP of the first day in the baseline period†, sustained for ≥ 2 calendar days.

*Daily minimum defined by lowest value of FiO_2 or PEEP during a calendar day that is maintained for > 1 hour

†Daily mimimum PEEP values of 0-5 cmH_2O are considered equivalent for the purposes of VAE surveillance.

⇩

Ventilator-Associated Condition (VAC)

⇩

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, the patient meets both of the following criteria:

1) Temperature > 38 °C or < 36 °C, OR white blood cell count ≥ 12,000 cells/mm^3 or ≤ 4000 cells/mm^3 AND
2) A new antimicrobial agent(s) is started, and is continued for ≥ 4 qualifying antimicrobial days (QAD)

⇩

Infection-related Ventilator-Associated Complication (IVAC)

⇩

On after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met (**taking into account organism exclusions specified in the protocol**):

1) Criterion 1: Positive culture of one of the following specimens, meeting quantitative or semi-quantitative thresholds† as outlined in protocol, without requirement for purulent respiratory secertions:
   - Endotracheal aspirate, ≥ 10^5 CFU/ml or corresponding semi-quantitative result
   - Bronchoalveolar lavage, ≥ 10^4 CFU/ml or corresponding semi-quantitative result
   - Lung tissue, ≥ 10^4 CFU/g or corresponding semi-quantiative result
   - Protected specimen brush, ≥ 10^3 CFU/ml or corresponding semi-quantitative result
2) Criterion 2: Purulent respiratory secretions (defined as secretions from the lungs, bronchi, or trachea that contain ≥25 neutrophils and ≤10 squamous epithelial cells per low power field [lpf, x100])† **PLUS** organism identified from one of the following specimens (to include qualitative culture, or quantitative/semi-quantitative culture without sufficient growth to meet criterion #1):
   - Sputum
   - Endotracheal aspirate
   - Bronchoalveolar lavage
   - Lung tissue
   - Protected specimen brush
3) Criterion 3: One of the following positive tests:
   - Organism identified from pleural fluid (where specimen was obtained during thoracentesis or initial placement of chest tube and NOT from an indwelling chest tube)
   - Lung histopathology, defined as: 1) abscess formation or foci of consolidation with intense neutrophil accumulation in bronchioles and alveoli; 2) evidence of lung parenchyma invasion by fungi (hyphae, pseudohyphae or yeast forms); 3) evidence of infection with viral pathogens listed below based on results of immunohistochemical assays, cytology, or microscopy performed on lung tissue
   - Diagnostic test for Legionella species
   - Diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus

†If the laboratory reports, semi-quantitative results, those results must correspond to the quantitative thresholds.

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Possible Ventilator-Associated Pneumonia (PVAP)

January 2020

Content source: Centers for Disease Control and Prevention

Source: ► https://www.cdc.gov/nhsn/pdfs/pscmanual/10-vae_final.pdf

Table 37.9 Comparison of adult and pediatric VACSource: Adapted from Cocoros et al. (2017)

Mechanically ventilated patient with ≥2 days of stability or improvement followed by Criterion 1 or 2 for ≥ 2 days

Adult VAC	**Pediatric VAC**
Increase in daily minimum Fio_2 by ≥0.20 or Increase in daily minimum PEEP of ≥3 cmH_2O	Increase in daily minimum Fio_2 by ≥0.25 or Increase in daily minimum MAP of ≥4 cmH_2O

Within 2 days before or after VAC onset (i.e. worsening oxygenation)

Adult IVAC	**Pediatric AVAC**
Patient meets both: • New antimicrobial agent(s) are started and continued for ≥4 days and • Temperature >38° C or < 36° C, or white blood cell count ≥12,000 or ≤4,000 cells/mm^3	New antimicrobial agent(s) are started and continued for ≥4 days*

Within 2 days meeting adult IVAC or pediatric AVAC criteria, patient meets one of the following criteria

Adult PVAP and Pediatric PVAP

Criterion 1*	or	Criterion 2*	or	Criterion 3*
Positive culture via endotracheal aspirate, BAL, lung tissue, or protected specimen brush with quantitative/semi-quantitative threshold		Purulent respiratory secretions *and* positive culture via specimens in Criterion 1, but not meeting those thresholds for growth		One of the following: organism identified via pleural fluid, lung histopathology, *Legionella* diagnostic test, or respiratory secretion positive for viral organism

To enhance diagnostic accuracy of healthcare-associated respiratory infections, methods for obtaining better *lower* airway and lung cultures have been developed and tested in adults. These include bronchoscopy-assisted bronchoalveolar lavage (BAL) with protected specimen brush (PSB) and non-bronchoscopy blind sampling with PSB. These methods have resulted in higher sensitivity and specificity, but have not been well tested in children due to technical and practical limitations of pediatric bronchoscopy including safe traverse of small endotracheal tubes with bronchoscopes, nonroutine use of BAL and blind PSB in PICUs, and inconsistent availability of pediatric bronchoscopists.

A comparative study has evaluated three ways to diagnose pediatric ventilator-associated infections using (1) clinical NNIS criteria; (2) blind, protected BAL without bronchoscopy to obtain quantitative cultures and Gram stains; and (3) nonquantitative cultures of endotracheal aspirates. The standard against which these three methods were compared was expert consensus opinion that VAP was present. This study found that blind, protected BAL was the most reliable diagnostic method (sensitivity 78%, specificity 86%). It has also been found that blind PSB plus BAL without bronchoscopy could be used in ventilated children to assist in antibiotic decision. It is recommended that the presence of intracellular bacteria (>1% of cells) was sufficient cause to institute broad-spectrum antibiotics. Subsequent quantitative results of PSB ($\geq 10^3$ CFU/mL = infection) and BAL ($\geq 10^4$ CFU/mL = infection) should guide more specific antibiotic selection. This study suggested that the presence of any one of these three microbiologic criteria was 90% sensitive for detecting pediatric VAP as compared to expert consensus. Absence of all three correctly ruled out VAP in 88% of patients compared to expert consensus.

The combination of blind BAL and PSB specimens with or without bronchoscopy appears to have the best sensitivity and specificity for diagnosing ventilator-associated pneumonia.

It is important to recognize that pediatric VAP negatively impacts outcome. VAP increases length of stay three- to fourfold, increases ventilator days two- to threefold, raises risk of tracheostomy, and is associated with an attributable risk of PICU mortality of 11% (odds ratio (OR) = 3.07). Adults with VAP are twice as likely to die than those without VAP and incur $10,000 higher hospital costs. Pediatric data suggest VAP incurs a direct cost of $51–56,000 per patient.

PICU-acquired viral respiratory infections are also associated with worse outcome. A multicenter Australian study matched children in the PICU with and without hospital-associated respiratory infection. Virus-positive patients had longer lengths of stay, longer duration, and higher incidence of invasive and noninvasive respiratory support (91% in virus-positive vs. 75% in virus-negative/untested patients) and more need for extracorporeal circulatory support (OR = 5.3), high-frequency oscillatory ventilation (OR = 3.0), and inhaled nitric oxide (OR = 2.7) compared to the virus-negative/untested group. However, there was no difference in outcomes between viral-positive and viral-negative patients when viral-positive patients were compared to only *tested* viral-negative patients (i.e., documented negative) suggesting other factors may be contributing to the difference. Enterovirus/rhinovirus followed by respiratory syncytial virus were the most common viruses isolated and did not demonstrate seasonal variability. One hundred twenty-one distinct viruses were cataloged in this cohort, and multiple viral pathogens were found in 20% of infected children.

Gram-negative organisms, especially *Pseudomonas aeruginosa*, cause most pediatric VAP.

Most VAPs are due to Gram-negative bacteria, especially *Pseudomonas aeruginosa* (29%), *Klebsiella pneumoniae* (15%), *Haemophilus influenzae* (9%), and enteric organisms. *Staphylococcus aureus* (12%) and yeast are also common (9%). Polymicrobial pneumonias may also occur in patients who are immunocompromised. Healthcare-associated viral pneumonias are less common, although certain pathogens such as respiratory syncytial virus, influenza, adenovirus, enterovirus, and human metapneumovirus occur and have devastating consequences among immunocompromised children. Viral acquisition among PICU patients brings attention to the role of fomites, strict hand hygiene, and universal precaution adherence in reducing HAI.

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37.5.1 Prevention

Factors contributing to infectious risk in intubated children include age, admission diagnosis, presence of pediatric acute respiratory distress syndrome (as defined by Pediatric Acute Lung Injury Consensus Committee), immunosuppressant drug exposure (including steroids), immunodeficiency, neuromuscular blockade, continuous or discontinuous opioid sedation, congenital syndromes, re-intubation, burns, tracheostomy, blood product transfusion, transport out of the PICU, presence of a central venous catheter, use of TPN, H_2-blockers, perioperative antibiotic prophylaxis, and bronchoscopy. Across studies, not all listed risk factors persist in multivariate analysis. A 2018 study using the modified pediatric VAC criteria demonstrated an incidence of 7 per 1000 ventilator days. Younger age and re-intubation were the only significant risk factors in multivariate analysis. Another study found that trauma was the only significant independent risk factor.

Micro-aspiration of oropharyngeal secretions and biofilm formation along the endotracheal tube are likely significant contributors to the development of ventilator-associated pneumonia.

Adult data suggest that micro-aspiration of oropharyngeal/gastric secretions, hematogenous spread, bacterial translocation from the gastrointestinal (GI) tract, desiccation of oral mucosa, and disruption of natural immune and mucosal barriers through trauma, burn, or surgery all contribute to healthcare-associated respiratory infections. The endotracheal tube itself, predisposed to

developing biofilms, provides passage to lower airways bypassing physical barriers afforded by glottic and supraglottic protection. Although these pathogenic mechanisms seem more likely to occur with uncuffed tubes, there is no clear data to confirm this. Placement of nasogastric tubes may aggravate bacterial colonization in the oropharyngeal area by creating sinusitis and increasing retrograde flow of bacteria-laden gastric refluxate. Gastric alkalization with H_2-blockers and proton pump inhibitors enhances bacterial colonization of the GI tract with virulent pathogens. Medical acid suppression, along with total time in reflux, strongly predicts development of VAP. Similarly, minimizing stress ulcer prophylaxis has been associated with reduction of adult VAP incidence by 38%. Gastric reflux may be less important than aspiration of oropharyngeal secretions, at least in adults. A schematic proposed pathogenesis is illustrated in Fig. 37.2.

Based on the proposed mechanisms of disease, preventive measures have been routinely instituted in adult ICUs and generally adopted by PICUs. Protocols include regular patient turning; maintaining head of bed at a 30° angle; oral chlorhexidine rinses; strict attention to universal precautions; aseptic and, ideally, in-line suctioning; prevention of gastric distention; and minimizing stress ulcer prophylaxis. This "bundle" reduced VAP in two adult ICUs and one pediatric ICU.

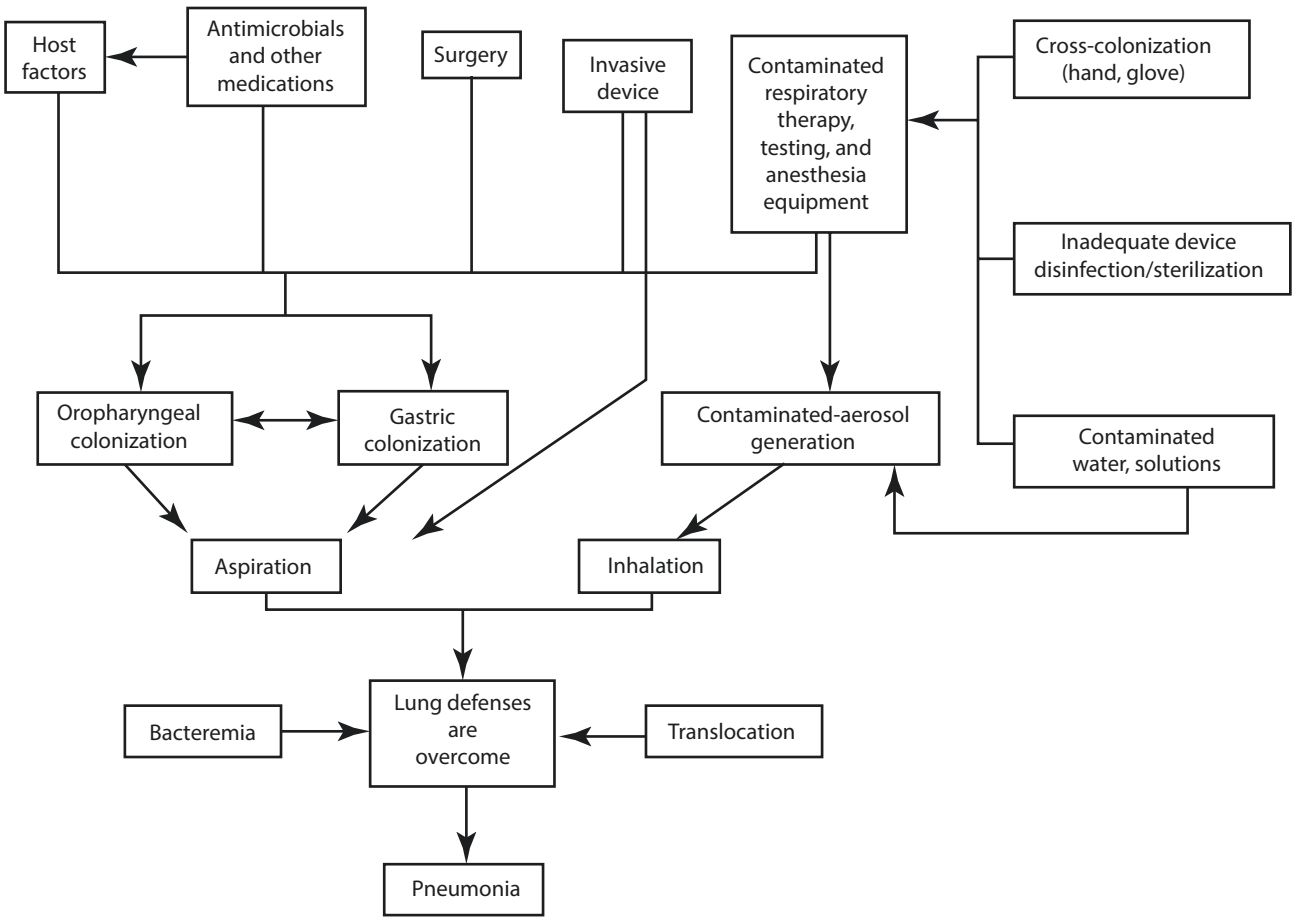

Fig. 37.2 Pathogenesis of nosocomial bacterial pneumonia. (Source: CDC, MMWR 1997)

Raising the head of the bed ≥30° is a key strategy in preventing ventilator-associated pneumonia.

Successful implementation of this and similar study protocols have prompted The Joint Commission and the Institute of Healthcare Improvement to recommend a multiple-component protocol to prevent VAP. As with other "bundled" care, it is not clear which of these interventions is the most important. The ventilator bundle contains the following:

- Raising the head of the bed to ≥30°
- Daily sedation "vacations" (reduce or turn off sedation briefly)
- Daily assessment of readiness to extubate
- Judicious peptic ulcer prophylaxis
- Deep vein thrombosis (VTE) prophylaxis

The first four interventions are likely applicable and reasonable in children, particularly as they directly attempt to reduce all ventilator days. Some institutions recommend VTE prophylaxis in children 12 years or older with at least sequential compression devices, but this remains variably practiced. The CDC has made additional recommendations regarding routine change in ventilator circuits (no more than once per week), humidification devices (heat and moisture exchangers are superior to heated-water humidification), aseptic in-line suctioning changes, etc. Chlorhexidine oral rinses to reduce oropharyngeal flora have been found useful in selected adult patients. Good oral hygiene care for ventilated PICU patients makes much physiologic sense and has been recommended, although not specifically studied.

One large children's hospital has developed a ventilator care bundle using a standard quality improvement approach (Plan, Do, Study, Act cycles). The bundle incorporated components of the adult ventilator bundle, the CDC guidelines for ventilator circuits, and data regarding oropharyngeal decontamination. Compliance with the bundle was associated with a decreased incidence of VAP from 5.6 per 1000 ventilator days to 0.3 per 1000 ventilator days ($p < 0.0001$). VAP-associated mortality in this study was 19%, further underscoring the importance of VAP prevention. The pediatric ventilator bundle used in this study is listed in ▶ Box 37.2.

Box 37.2 Pediatric ventilator bundle

Prevention of bacterial colonization of the oropharynx, stomach, and sinuses

- Change ventilator circuits and in-line suction catheters *only* when visibly soiled
- Drain condensate from ventilator circuit at least every 2–4 h (use heated wire circuits to reduce rainout)
- Store oral suction devices (when not in use) in non-sealed plastic bag at the bedside; rinse after use
- Hand hygiene before and after contact with ventilator circuit
- When soiling from respiratory secretions is anticipated, wear gown before providing care to patient
- Follow Unit Mouth Care Policy – every 2–4 h

Prevention of aspiration of contaminated secretions

- Elevate HOB 30–45°, unless contraindicated and by written order
- Always drain ventilator circuit before repositioning patient
- When possible, for children >12 years old, use endotracheal tubes with dorsal lumen above endotracheal cuff to help suction secretions above the cuff

Source: Adapted from Bigham et al. (2009)

37.5.2 Treatment

Initial antibiotic treatment of suspected ventilator-associated infection should be broad spectrum based on the most likely organisms. Gram-negative organisms comprise >50% of VAP. Antipseudomonal antibiotics such as cefepime, piperacillin-tazobactam, or meropenem should be used empirically. Vancomycin is appropriate for initial, empiric, Gram-positive coverage. After 48 h, if cultures do not suggest infection, the chest radiograph is clear, and pulmonary compliance and oxygenation have not worsened, antibiotics should be stopped. Unnecessary antibiotic exposure leads to patient morbidity and higher rates of bacterial resistance in the hospital environment. Suspected ventilator-associated infection is responsible for the most antibiotic use in the PICU as well as the most superfluous antibiotic use. This further indicates the role of better delineation of true HAI of the respiratory system and proper antibiotic stewardship. If infection is present, a 5–10-day course of antibiotics is generally appropriate, the exact length depending on the type of infection (e.g., VAT vs. VAP), the organism to be covered, the patient's immunological competence, and the severity of illness.

37.6 Urinary Tract Infection

Urinary catheters are used in the PICU most commonly for the meticulous measurement of urine output. With each catheter day, there is a 5–8% increased risk of a urinary tract infection. Comparative risks versus benefits of continued catheter use should be assessed frequently. Healthcare burden of catheter-associated urinary tract infection (CAUTI) in pediatrics is not completely defined. In adults, CAUTIs contribute to morbidity, increase hospital stay by 1–4.5 days, and result in death in 2.3% of cases. This equates to 13,000 deaths annually. Among children, one cohort of matched PICU patients with CAUTI demonstrated an increase in baseline mortality from 5% to 17%, a 9-day longer PICU length of stay among survivors, and an increased mechanical ventilation duration by 1 week. Hospital stay increased by an average of 29 days and hospital costs incurred doubled.

Urinary catheter biofilm secreted by adherent bacteria resists removal by washing and protects bacteria from being killed by antimicrobial therapy.

In neonatal intensive care units, urinary tract infections are not associated with indwelling catheters as only 12% of patients with UTI have catheter exposure. This suggests that healthcare-associated UTI in neonates has a different pathogenesis than in children and adults where UTI is almost exclusively associated with catheters. Intra- and extraluminal biofilms play a central role in pathogenesis. In the case of CAUTI, the biofilm can be up to 400 organisms deep and resists removal by simple washing. Bacteria in the biofilm can hydrolyze urea, alkalinizing urine and resulting in mineral precipitation sufficiently large that catheter lumens are obstructed. Biofilms result in an initial asymptomatic bacteriuria. Subsequently, some patients develop a true urinary tract infection with inflammation; some progress to develop fulminant sepsis. Bacteria originating from the GI tract either infect the urinary tract directly during catheter insertion or migrate from the perineal area into the bladder via the mucus sheath surrounding the external catheter wall. Direct contamination of the collecting system, usually via the hands of healthcare providers, allows intraluminal introduction of bacteria. Obstructed or slow urine flow, glycosuria, colonization with resistant organisms, yeast in the urine, urethral trauma, and compromised immunologic function all contribute to CAUTI.

To ensure accurate diagnosis and management of a CAUTI (affects antibiotic stewardship, decisions about catheter removal, imaging studies, etc.), opti-

mal sterility of sample collection is essential. Precise definitions of a urinary tract infection are made based on colony-forming units (CFU) and other biochemical data obtained from these samples. Specimens obtained sterilely by bladder catheterization and suprapubic aspiration or from the side port of an existing urinary catheter (using chlorhexidine or alcohol to wipe ports and allowing drying, along with sterile equipment) are optimal, since there is less likelihood of contamination. Unnecessary antibiotic exposure should be avoided although this is weighed against a 2–3% incidence of sepsis in patients without adequate or no treatment of true urinary tract infections. The NHSN of the CDC has defined CAUTI as noted in ◘ Table 37.10.

However, there are children in whom the application of these criteria is insufficient to make a diagnosis (low sensitivity), and yet, they have a urinary tract infection. Missing these CAUTIs with their potential for causing urosepsis is obviously problematic. Based in part on the CDC surveillance definitions, the International Forum on Sepsis in Children has proposed more pragmatic definitions in critically ill children (► Box 37.3).

Box 37.3 Definitions of urinary tract infection in critically ill children

Definite UTI

- Symptoms (fever >38 °C or urinary tract symptoms) or sepsis not due to another infection PLUS
  - Urine culture ≥100,000 CFU/mL of no more than two species *or*
  - Urine culture ≥50,000 CFU/mL from catheter specimen, single organism, *and* urinary WBC count of >10/μL (unspun urine)
- No symptoms PLUS
  - Urinary catheter within previous 7 days of single culture PLUS culture of >100,000 CFU/mL of no more than two species *or*
  - No urinary catheter within previous 7 days of culture PLUS two separate cultures of ≥100,000 CFU/mL of the same organism with no more than two species present

Probable UTI

Symptoms and no urinary catheter present *and* ≥10 WBC/high-power field unspun urine *and* any organisms on unspun urine *or* >10,000 CFU/mL on catheter specimen

Possible UTI

Symptoms and no urinary catheter present *and* either

- Urinary dipstick positive for leukocyte esterase or nitrites
- ≥ 10 WBC/high-power field of unspun urine
- Any organisms seen on Gram stain of unspun urine

Source: Adapted from Langley (2005)

UTI urinary tract infection, *CFU* colony-forming units, *WBC* white blood cell

Gram-negative bacteria and yeasts are the most common causes of urinary tract infection in PICU patients.

The most common UTI-associated pathogens are Gram-negative bacteria (*Escherichia coli*, *Proteus* species, and *Enterobacteriaceae*) and yeast, the combination accounting for approximately 80% of pathogens. Yeast is typically *Candida* species and in some studies is responsible for over 40% of isolates, although notably it is considered "nonpathogenic" by CDC criteria. Gram-negative organisms account for most others, including *Pseudomonas*, *Klebsiella*, and *Citrobacter* species. Treatments of healthcare-associated urinary tract infection (HA-UTI) and CAUTI contribute to antibiotic resistance interna-

Table 37.10 NHSN definition and diagnostic criteria for CAUTI

Criterion	Symptomatic UTI
CAUTI > 1 year of age	Catheter exposure >2 consecutive days in the PICU on the date of the event AND catheter was either present for any portion of the calendar day of the event or removed the day before the event
	At least one of the following signs/symptoms Temperature > 38.0 °C Suprapubic pain, tenderness CVA pain or tenderness Urinary urgency Urinary frequency Dysuria Urine culture with *no more than* two organisms with at least one of which must have 10^5 CFU/mL *Candida*/yeast cannot be considered a pathogen
CAUTI ≤ 1 year of age	Catheter exposure >2 consecutive days in the PICU on the date of the event AND catheter was either present for any portion of the calendar day of the event or removed the day before the event At least one of the following signs/symptoms Fever (>38.0 °C) Hypothermia (<36.0 °C) Apnea Bradycardia Lethargy Vomiting Suprapubic pain/tenderness Urine culture with *no more than* two organisms at least one of which must have 10^5 CFU/mL *Candida*/yeast cannot be considered as a pathogen

NHSN National Healthcare Safety Network, *CAUTI* catheter-associated urinary tract infection, *PICU* pediatric intensive care unit, *CVA* costovertebral angle, *CFU* colony-forming units

tionally. Adult studies demonstrate geographic variation in resistance, making knowledge of local organisms' prevalence, antibiotic sensitivity, and patient history of infections critical. Gentamicin-resistant *Enterococcus* is found frequently, as well as extended-spectrum beta-lactamase (ESBL) Gram-negatives. Gram-positive organisms are not common sources of UTI in pediatric critically ill patients. The diagnosis of fungal urinary tract infections is especially difficult, and it is not clear whether the same diagnostic criteria detailed above should be used. In some immunocompromised children for whom fungemia is life-threatening, *Candida* UTI should likely be treated and should prompt catheter removal. Other children at greater risk for urinary tract infection are those undergoing cardiac surgery (relative risk = 2.7) and patients with underlying neurologic disease.

37.6.1 Prevention

Since biofilms represent the predominant pathogenic mechanism for CAUTI, prevention strategies surround biofilm reduction and limiting device days. Careful selection of patients for urinary catheter insertion is the first step, weighing the benefits and risks. The most common reasons cited for catheter use by a surveyed group of experienced intensivists include shock, fluid overload, perineal edema, known difficulty with catheterization, and known need

for re-catheterization due to urinary retention. Factors significantly associated with device removal were extubation, fever, and history of HA-UTI/CAUTI and PICU stay >7 days. Sterile placement of a urinary catheter with maintenance of a closed urinary system is the next step to avoid introduction of bacteria. Due attention to insuring unobstructed urine flow has helped adult patients and is likely to be important in children. Minimizing urinary catheter duration is perhaps most important. Some studies report that catheter use is inappropriately prolonged in up to 50% of patients. CAUTI incidence increases exponentially after device exposure >48 h and is limited substantially when catheters are removed within 48–72 h. Reminders on daily rounds to address the ongoing need for the urinary catheter reduce catheter days significantly with a simultaneous decrease in UTIs. Similarly, PICU safety champions that focus on decreasing CAUTI have been found to be effective. Other attempts to reduce CAUTI such as the use of silver alloy-coated catheters, prophylactic antibiotics, bladder irrigations, or routine catheter changes have not shown consistent benefit in adults.

37.6.2 Treatment

The treatment of CAUTI involves catheter removal whenever possible. Preliminary antibiotic selection for a suspected urinary tract infection should focus on Gram-negative organisms and consider that a higher percentage of common organisms leading to CAUTI may have antibiotic resistance compared to other HAIs. Treatment with appropriate antibiotics for 7–14 days for complicated UTI is considered appropriate and should be accompanied by catheter removal. Uncomplicated UTI can be treated for 5 days. Although a substantial number of urinary tract isolates are yeast, most practitioners do not recommend starting antifungal agents either via bladder instillation or systemically until there has been confirmation of the infection and/or the presence of systemic symptoms.

37.7 Special Populations

37.7.1 Surgical Patients

Surgical patients in the PICU have often undergone significant corrective procedures. These postoperative patients frequently require invasive devices for monitoring, for complicated fluid, hematologic, and hemodynamic management, and for mechanical ventilation. Patient-associated factors such as immunologic derangement and aberrancy associated with some of these operations, such as cardiopulmonary bypass during cardiac surgery and the pharmacotherapy required for solid organ transplant, make surgical patients a special high-risk population for HAI.

Consideration of surgical wound infections is applicable to several types of surgery: abdominal, otolaryngologic, orthopedic, urologic, neurosurgical, trauma, and cardiac being most common in the PICU. Surgical wound infections may be divided into superficial and deep infections. Superficial infections involve the skin and subcutaneous tissues and symptoms include pain, warmth, and edema. At times, these infections require surgical opening of the wound. In contrast, deep surgical site infections penetrate further into incised tissue and are characterized by purulent drainage from the deep part of the incision (but not from an "organ-specific" space), with signs and symptoms of an infec-

tion. These deep infections more often necessitate debridement. Detailed data regarding nosocomial infections in each specific type of surgical patient admitted to the PICU are scant, but a few types merit discussion.

37.7.1.1 Cardiothoracic Surgery

Recently, because of unique complexity, physiology, and high volume, there has been a trend to identify pediatric cardiac surgery patients as a distinct ICU population, often residing in designated pediatric cardiac ICUs (CICUs).

Between 2% and 8% of pediatric cardiac surgical patients develop a surgical wound infection. The large majority of these are caused by either S*taphylococcus aureus* or coagulase-negative staphylococci.

Several studies in the early 2000s reported an approximately 16% incidence of nosocomial infections in pediatric cardiac surgery patients, with bloodstream infections (5–10%) and wound infections (2–8%) accounting for most of these. The most common causes of bacteremia were Gram-negative organisms (*Klebsiella* species 22%, *Enterobacter* species 17%, *Pseudomonas* species 16%). Staphylococci also contributed significantly (coagulase-negative staphylococci 11%, *Staphylococcus aureus* 5%). A retrospective review of 22,839 CICU encounters from 2013 to 2016 in North America revealed an occurrence rate of 2.4% for developing any HAI, a rate of approximately 3.3 HAIs per 1000 CICU days. Seventy-three percent of these occur in children <1 year of age. The incidence of HAI was twice as high in surgical versus nonsurgical encounters and resulted in longer lengths of stay and increased mortality (24.4% compared to 3.4% mortality in HAI-free patients). Significant risk factors for developing a nosocomial infection include prematurity, presence of a congenital anomaly, admission with an active medical condition, and high surgical complexity. The highest complexity surgeries, defined by a STAT (Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery) score of 4–5, are associated with an odds ratio of 4.0 for HAI. An ICU stay >48 h, the need for an open chest after surgery, and extracorporeal membrane oxygenation are also important risk factors. Multivariate analysis reveals that patients with high surgical complexity have a significant risk for HAI with STAT 4–5 patients incurring 54% of all surgical HAI and 64% of all surgical encounter CLABSI.

Cardiac surgery patients who have undergone deep hypothermic circulatory arrest (< 20 °C) have a 20-fold higher risk of developing a surgical site infection.

Four studies spanning over 15 years involving pediatric cardiac surgery patients demonstrate that most wound infections (superficial, deep incisional, sternal, or mediastinitis) are due to *Staphylococcus aureus* (40–66%) and coagulase-negative staphylococci (10–25%). Wound infections due to yeast are very uncommon. Risk factors for wound infection are illustrated in ▶ Box 37.4. Some factors are unavoidable but are mentioned to promote a high index of suspicion when confronted by that patient. For example, deep hypothermic circulatory arrest (<20 °C) required for certain surgeries is associated with a 20-fold increased risk of surgical wound infection (▶ Box 37.4).

Box 37.4 Wound infection risk factors in pediatric cardiac surgery patients

- Age <1 month
- Longer surgery (4 h vs. 2.5 h)
- Deep hypothermic circulatory arrest (20-fold increased risk)
- Preoperative hospitalization (>1 day)
- Postoperative pCO_2 > 50 mmHg
- Bleeding necessitating re-exploration
- Postoperative open chest
- Duration of central venous catheter (4 days vs. 2 days)
- Duration of ventilatory support

Reduction of HAI in pediatric cardiac surgery patients is possible. With optimized, routine wound and device care, one group reduced wound infections from 7% to 4.3%, chest tube infections from 3.5% to 0.6%, CLABSIs from 4.5% to 3.2%, CAUTIs from 1.6% to 0.2%, and lower respiratory tract infections from 2.2% to 0.6%. Prevention of HAI in cardiac surgery patients is further improved by device removal (central venous catheters, ventilators, urinary catheters, and chest tubes) within 24–48 h of placement, minimizing preoperative hospitalization, prompt closing of open chests, and, in at least one study, prophylactic antibiotics (cefazolin) until the chest tubes are removed.

37.7.1.2 Neurosurgery and Craniofacial Surgery

A significant number of PICU patients require admission secondary to traumatic brain injury. These patients may require an intracranial pressure monitoring device to facilitate management, and therefore, intracranial HAIs may occur. These infections may originate anywhere along the tract of the monitor, including the meninges, the brain, or the cerebrospinal fluid. Adult incidence of ventriculostomy-related infection in the setting of trauma has been estimated to be between 11% and 19%; in other meta-analyses, the incidence is reported to be 10.6–11.4 per 1000 catheter days. Risks associated with HAI are cranial fracture with cerebrospinal fluid (CSF) leak, subarachnoid hemorrhage, and length of days that the catheter is in place. The precise relationship of ventriculostomy duration to infection is unclear. Some studies report a plateau incidence of HAI after 5–10 days, and others find that HAI is completely unrelated to device duration. One meta-analysis of 35 primarily adult studies reported a pooled external ventricular drain infection rate of 19.6 per 1000 catheter days with catheter duration of less than 7 days, 12.8 per 1000 catheter days for drains in place for 7–10 days, and 8 per 1000 catheter days for drains in place for more than 10 days. Gram-negative organisms such as *Klebsiella* and *Enterobacter* species appear to predominate slightly in some studies, but *Staphylococcus aureus* and coagulase-negative *Staphylococcus* are also common. *Candida* species are also reported.

Between 10% and 20% of intracranial monitoring devices become infected.

Routine changes in intracranial pressure monitoring devices, prophylactic antibiotics throughout the duration of use, and routine daily cerebrospinal fluid cultures are not recommended.

The Infectious Diseases Society of America (IDSA) in 2017, in conjunction with adult and pediatric neurosurgical input, did not recommend routine surveillance cultures of devices in place for CSF drainage not involved in treating an intracranial infection. For identification of healthcare-associated ventriculitis, they recommended using CSF cell counts (>15 WBC/HPF), CSF lactate (>4 mmol/L), and CSF procalcitonin (>1 ng/mL) as biomarkers. In one cited study, elevation of these markers predicted all cases of central nervous system (CNS) infection. Cerebrospinal fluid protein, glucose, and the peripheral WBC count are not reliable indicators of CNS infection. Increasing CSF white cell count is more sensitive, but not completely predictive as 20% of patients with brain infection had a normal CSF white count and lactate in one adult study. One adult study found that a combination of CSF procalcitonin >0.075 ng/mL and CSF lactate >3.45 mmol/L was 96% sensitive for detecting healthcare-associated ventriculitis in the postoperative period and the absence of these markers carried a 97.6% negative predictive value. However, there are minimal data on pediatric patients. Routine changes of functioning ventricular catheters have not been found to be of value in preventing infection (and may even worsen them), nor has the continuous use of antibiotics during the time of drain use. In some studies, this practice selected for resistant Gram-positive, Gram-negative, and *Candida* infections.

Children in whom long-term hydrocephalus management requires ventriculoperitoneal (VP) shunts differ from patients with an acute need for ventricular or intracranial device placements. These long-term VP shunts experience

infectious complications 2.8–14% of the time at and around the time of placement. Among all patients with VP shunts, there is a 4–17% annual incidence of infection, although this is quite variable across studies. Risk factors for VP shunt infections include prematurity, previous intraventricular hemorrhage, younger age, previous shunt infection, and a shunt required to manage previous meningitis, ventriculitis, and myelomeningocele. Other factors may also increase risk such as the neurosurgeon's experience, catheter placements below T7, the number of people entering the operating room during the surgery, the length of surgery, and a history of shunt revision with >3 revisions being particularly predictive of complications. Double gloving, antimicrobial impregnated sutures and shunts (commonly clindamycin, rifampin, minocycline), periprocedural prophylactic antimicrobial administration, and routine external ventriculostomy device (EVD) care bundles are all protective against infection.

The most common cause of VP shunt infection is colonization at the time of surgery, followed by retrograde infection of the distal end of the catheter, typically in the peritoneal cavity. The latter pathogenesis is more likely in patients with myelomeningocele and those who require multiple abdominal surgeries. At times, the diagnosis of a VP shunt infection is challenging since the most common pathogens involved, coagulase-negative staphylococci and *Propionibacterium acnes*, are indolent and not associated with overt inflammation. Providers should have a high index of suspicion for patients with VP shunt presenting with new headache, change in mental status, lethargy, nausea, tenderness or erythema over subcutaneous shunt tubing, evidence of peritonitis, or fever with no other obvious source. The first four symptoms are present in 65% of patients with shunt infection. Fever is notably variable in this population reported in as few as 14% and as many as 90% of patients depending on the report. The 2017 IDSA guidelines strongly recommend that the absence of fever does not rule out shunt infection in children presenting with other concerning symptoms.

► Box 37.5 lists the CDC/NHSN definition for healthcare-associated ventriculitis or meningitis as well as definitions for colonization and contamination of shunts.

Box 37.5 NHSN definition for healthcare-associated ventriculitis

- *Contamination*: An *isolated* positive CSF culture or Gram stain, with normal CSF cell count and glucose and protein concentrations and with lack of clinical symptoms suspicious for ventriculitis or meningitis
- *Colonization*: *Multiple* positive CSF cultures or Gram stains, with normal CSF cell count and glucose and protein concentrations and with lack of clinical symptoms suspicious for ventriculitis or meningitis
- *Infection*: Single or multiple positive CSF cultures with CSF pleocytosis and/or hypoglycorrhachia, or an increasing cell count, and clinical symptoms suspicious for ventriculitis or meningitis. The patient must satisfy at least *one* of the following three criteria:
  (1) Organism cultured from the CSF or positive nonculture-based microbiologic testing performed for the purpose of diagnosis or treatment
  (2) **For patients > 1 yr:** At least two of the following symptoms with no other recognized cause:
  - Fever >38 °C OR headache*
  - Meningeal signs
  - Cranial nerve signs

- AND at least one of the following
- Increased white cells, elevated protein, and decreased glucose in CSF
- Organisms seen on Gram stain of CSF
- Organisms cultured from blood or positive nonculture-based microbiologic testing performed for the purpose of diagnosis or treatment
- Diagnostic single-antibody titer (immunoglobulin M) or fourfold increase in paired sera (immunoglobulin G) for organism

(3) **For patients ≤ 1 yr:** At least two of the following symptoms with no other recognized cause:

- Fever >38 °C, hypothermia <36 °C, apnea, bradycardia, OR irritability*
- Meningeal signs
- Cranial nerve signs
- AND at least one of the following
- Increased white cells, elevated protein, and decreased glucose in CSF
- Organisms seen on Gram stain of CSF
- Organisms cultured from blood or positive nonculture-based microbiologic testing performed for the purpose of diagnosis or treatment
- Diagnostic single-antibody titer (immunoglobulin M) or fourfold increase in paired sera (immunoglobulin G) for organism

Source: CDC/NHSN Surveillance Definitions; January 2015
NHSN National Healthcare Safety Network, *CSF* cerebrospinal fluid
*Elements of this bullet point alone may not be used to meet the two required elements

If a HAI of a ventricular drain or VP shunt is suspected, empiric antibiotics should include an antipseudomonal agent with good CNS penetration (cefepime, ceftazidime, and meropenem over piperacillin-tazobactam) and vancomycin for Gram-positive coverage. CSF culture sensitivity decreases from 88% to 70% in children receiving antibiotics prior to CSF collection and to 59% if antibiotic duration is >24 h prior to obtaining CSF culture. A blood culture should be obtained simultaneously understanding that for VP and ventriculo-pleural shunts, the incidence of negative blood culture approaches 80%, as compared to ventriculoatrial shunts where 90% of patients demonstrate bacteremia on culture. Coagulase-negative *Staphylococcus*, *Propionibacterium acnes*, *Staphylococcus aureus*, Gram-negative organisms including *Escherichia coli*, and *Klebsiella* species are most commonly isolated. Among immunocompromised patients, premature infants, and those with multiple previous neurosurgical procedures, *Candida*, *Aspergillus*, and *Cryptococcus* can be found. In addition to removal of some or all parts of the shunt and placement of a new drain, 10–14 days of anti-infective therapy from the first negative culture is generally recommended. Consultation with infectious disease specialists is generally recommended and essential for complicated bacterial or fungal disease.

Neurosurgical patients undergoing craniofacial reconstructions have a 3% incidence of surgical site infection with the most complex lesions at highest risk (OR = 13). Meningitis can also occur in the post-craniotomy setting, and the use of a CSF drain, a CSF leak, and perioperative steroid use increase the risk of postoperative meningitis.

37.7.1.3 Burns

Pediatric burn patients have lost the barrier protection that the skin affords and suffer physiology similar to a chronic open wound. Direct exposure of bacteria to injured subepithelial and dermal tissues is more likely to result in bacterial invasion. This loss of protection coupled with multiple other factors contributing to the immunocompromised state of burned patients places them at high risk of infection. Burn patients are frequently neutropenic, demonstrate depressed neutrophil and T-cell function, and have compromised microvascular circulation and thrombotic complications, increased gut permeability to bacterial organisms, low immune protein production, and poor nutritional status which all further augment risk. In addition, these patients require many devices associated with nosocomial infections – intravascular catheters, endotracheal tubes/tracheostomies, urinary catheters, hemodialysis catheters, and chest tubes. Consequently, infection is the most common cause of death in patients with burns.

However, the diagnosis of HAI in burn patients is challenging. Noninfectious fever is common, wound assessment difficult, and white blood cell counts may not be elevated. Frequent, brief courses of antibiotics for "rule outs" may result in colonization of resistant organisms which then invade the patient. A high index of suspicion is required, and careful adherence to standardized definitions and strict antibiotic stewardship may be helpful. Early and optimal enteral nutrition reduces infection risk. Prophylactic antibiotics and gastric decontamination have not proven useful in reducing infection.

The most common HAIs in pediatric burn patients are urinary tract infection and wound infection although these patients experience higher rates of all HAIs.

The epidemiology of HAIs in burn patients is unclear since the NNIS database does not break out pediatric burn patients as a special population. However, comparison of burn ICUs to other ICUs generally demonstrates a higher rate of HAIs; reported incidences of HAI in burn ICUs range from 14 to 63%. Of these, UTI is most common (44%), followed by wound infection (32%), pneumonia (20%), and bloodstream infection (7%). Total burn surface area is directly related to the risk of developing a burn wound infection.

The highest *device-related* incidence of nosocomial infection in burn patients is VAP (55 per 1000 ventilator days) and CAUTI (42 per 1000 device days). This is an 18-fold and 8-fold increased incidence, respectively, compared to general PICU patients. At the time of that report (2002), CLABSIs were reported to occur at a rate of 9 per 1000 catheter days compared to 7 per 1000 for general PICU patients. Given that the CLABSI incidence has now decreased from approximately 7 per 1000 to 1 per 1000 catheter days in general PICU patients (◘ Table 37.2), it may be that the CLABSI incidence for burn patients is also lower. The use of implementation science to decrease CLABSI in burn patients has been reported in adults with an incidence of 15 per 1000 catheter days decreasing to zero over a period of 2 years. Infections are most commonly due to *Staphylococcus aureus* (20%), *Pseudomonas* (15%), *Enterococcus* (12%), and *Escherichia coli* (12%).

Due to elevated device-related risk, sterile insertion and maintenance with prompt removal when no longer needed should improve patient outcome and reduce morbidity and mortality. Fastidious attention to infection control practices such as handwashing and gloving is important. Cellulitis, burn impetigo, burn-related surgical wound infection, and invasive burn wound infection can be decreased by proper timing of dressing changes with attention to prevention of drying, application of sufficient antibacterial/moisturizing agents, timely wound debridement, and early wound closure including grafting.

37.7.2 Immunocompromised Patients

An adequate immunologic response is a critical factor in the risk for developing infections and responding appropriately to them. Immunocompromised patients such as those undergoing solid organ transplantation, hematopoietic cell recipients, those with congenital immunologic deficits, acquired immunodeficiency syndrome (AIDS), autoimmune disease, and cancer, and those receiving immunosuppressive medications are at higher risk for infection, including healthcare-related infections, than patients who are immunocompetent. These patients may be neutropenic, lymphopenic (decreased T-cells), unable to produce adequate immunoglobulins and antibodies, and/or have altered cellular mechanisms which interfere with effective immunologic function such as dysregulation of cytokine production.

Immunocompromised pediatric patients are more likely to sustain both viral and bacterial HAIs with higher morbidity and mortality. Respiratory syncytial virus (RSV), parainfluenza virus, adenovirus, and norovirus HAIs have all been described in immunocompromised patients with significant morbidity/mortality especially in patients with RSV and adenovirus. Given the high prevalence of RSV each year in hospitals and the ease of spread, this is particularly of concern. In one study, as many as 36% of hospitalized RSV-positive immunocompromised children acquired it while in the hospital, and of these, 24% required intensive care. Bacterial HAIs also commonly develop in these patients because they are not only immunocompromised, but they also require devices for the provision of critical care (central venous catheters, endotracheal tubes, urinary catheters, arterial catheters, etc.). In addition, once sufficiently ill to require prolonged intensive care, they likely have developed additional critical illness stress-induced immunosuppression (see below). Efforts to reduce nosocomial infections in these patients by providing daily nutritional supplements (zinc, selenium, glutamine) along with metoclopramide show promise. In a *post hoc* analysis of the Pediatric CRISIS Prevention Trial (2012), this treatment reduced nosocomial infection rates from 6.33 per 100 days to 1.57 per 100 days in the small cohort of immunocompromised children ($n = 27$).

A second group of patients with immune dysregulation has now been found to have a significant likelihood (up to 50% risk) of acquiring PICU-related HAIs. These patients have critical illness-induced innate immunosuppression and are typically characterized by a prolonged ICU stay (>3 days), presence of invasive devices, and dysfunction of at least two organ systems (multi-organ dysfunction syndrome or MODS). Diagnoses may vary and include sepsis secondary to infection, trauma, cardiopulmonary bypass, surgery, and other inflammatory states. Not only do these patients have a high level of inflammation with production of pro-inflammatory cytokines, but concomitantly have a significant compensatory anti-inflammatory response syndrome (CARS) with an increase in anti-inflammatory cytokines. This *immunoparalysis* is quantifiable by either (1) measuring expression of HLA-DR (human leukocyte antigen DR), a monocyte cell surface molecule, and finding it to be less than 30% or (2) measuring tumor necrosis factor-α (TNF-α) after *ex vivo* whole blood monocyte stimulation with lipopolysaccharide, resulting in a value less than 200 pg/mL. Patients who exhibit immunoparalysis according to this definition have an increased risk (RR = 3.3) of developing a nosocomial infection and a death (RR – 5.8).

Awareness of the compromised immune state of many PICU patients and its role in increasing the risk of nosocomial infection should encourage meticulous attention to all preventive strategies currently recommended.

Immunocompromised patients and those with critical illness-induced innate immunosuppression (immunoparalysis) have a higher incidence of nosocomial viral and bacterial infection. Preventive measures are especially important in this special population.

37.7.3 *Clostridium difficile* Infections (CDI)

Clostridium difficile infection (CDI) is caused by a Gram-positive, endospore-forming, anaerobic, toxin-producing gastrointestinal bacillus. There is a variable to high level of carriage (2.5–90%) of this organism in healthy children, particularly in those less than 2 years of age. However, *Clostridium difficile* infection can occur in children and may lead to complications including bleeding, pseudomembranous colitis, toxic megacolon, and death. Severe infection occurs in 8% of children. Patients with abdominal surgery and those with gut failure and TPN dependence represent special at-risk populations for the development of healthcare-acquired CDI (HA-CDI). CDI is the most common cause of nosocomial diarrhea. However, children infrequently present with diarrhea alone; most also present with fever (49–84%) and abdominal pain (42–55%). More than half (55%) have signs of volume depletion and tachycardia, while 37% present with vomiting and 12.5–25% with grossly bloody stools. The CDC tracks CDI in the United States and reports 14,000 deaths annually related to CDI with an associated 1 billion dollar cost. A point-prevalence study of 183 US hospitals found that CDI comprised 12.1% of HAI. Data also suggest that the incidence of this infection is increasing in adults as are drug resistance patterns associated with the *Clostridium* spores.

Risks for developing CDI include hospitalization, especially for those with prolonged hospital length of stay, as well as antibiotic exposure particularly clindamycin, fluoroquinolones, and cephalosporins. Some studies demonstrate an increased risk of CDI with gastric acid suppression by proton pump inhibitors, although this has not been consistently demonstrated in children. Chronic, underlying disease likely leading to exposure to the above risk factors, frequent medical and procedural exposures, chronic medication use, higher rates of gastric or jejunal feedings, and the presence of an ileostomy or colostomy are all associated with CDI. One study has reported that 69% of cases of CDI were in children with at least one comorbid complex, chronic condition.

Conditions associated with pediatric HA-CDI include malignancy, hematopoietic cell transplant, TPN dependence, asthma, inflammatory bowel disease, and gastric reflux. There is a 20–30% recurrence rate of CDI as defined by return of symptoms and positive stool study within 60 days of treatment. In a pediatric review, malignancy (OR = 3.9), recent surgery (OR = 2.4), and the number of antibiotic exposures across classes (OR = 1.33) were significantly associated with higher recurrence in multivariate analysis. Within that cohort, after one recurrence, 30% of patients went on to have multiple recurrences.

Initial recommended treatment for *mild to moderate* CDI in children is enteral metronidazole rather than enteral vancomycin. Metronidazole costs less and appears to be equally effective, and there is concern for the development of increased vancomycin-resistant *Enterococcus* in at-risk groups. *Severe* CDI should be treated with intravenous metronidazole and enteral vancomycin. Metronidazole has a higher treatment failure rate than vancomycin (22.4 vs. 14.2%) but a similar incidence of recurrence (27 and 24%).

37.8 General Principles for the Prevention and Diagnosis of Healthcare-Associated Infections

37.8.1 Maintain Good Hand Hygiene

There is a lack of prospective, randomized trials demonstrating the precise impact of handwashing on HAI in all populations. However, certain PICU

populations are disproportionately affected by poor and excellent hand hygiene. For example, attention to good hand hygiene may reduce HAI by 40% in post-solid organ transplant PICU patients. Other research suggests that meticulous handwashing may reduce HAI caused by methicillin-resistant *Staphylococcus aureus*. The variable effect of hand hygiene in reducing HAI is likely because many nosocomial infections are secondary to a patient's own organisms, and spread of organisms by healthcare providers is variable, depending on the organism density on their hands.

The CDC has issued a comprehensive set of recommendations about hand hygiene in healthcare settings. These guidelines include a summary of all aspects of hand hygiene including scientific evidence for its effectiveness as an intervention, as well as evidence about techniques, types of cleansing/disinfecting substances, and compliance by healthcare providers.

Isopropyl alcohol (concentrations of >60%) handwashes are effective in eradicating bacteria, viruses, and fungi on caregivers' hands.

Healthcare providers' adherence to handwashing guidelines is notoriously poor, with physicians exhibiting the worst compliance. Easy accessibility of isopropyl alcohol-based handwashes in wall dispensers has improved compliance even among this group. Alcohol-based solutions are especially attractive since isopropyl alcohol in concentrations >60% effectively kills Gram-positive and Gram-negative bacteria, enveloped and non-enveloped viruses (herpes, influenza, RSV, hepatitis A, rotavirus, etc.), and some fungi. In addition, alcohol evaporates quickly and does not require additional containers for effective use. Mixed in gels at over 60%, irritation to the hands is minimal.

37.8.2 Follow Standard Isolation Practices

Spread of organisms among ICU patients has been described frequently and is typically caused by staff carriage of organisms on hands and/or gloves, carriage of organisms on fomites such as stethoscopes, droplet nuclei spread by air currents, and/or contact with visitors. Outbreaks of RSV, enterovirus, *Clostridium difficile*, *Stenotrophomonas*, methicillin-resistant S*taphylococcus aureus*, vancomycin-resistant *Enterococcus*, and influenza have been reported. Suspicion or evidence of transmittable infection must be followed by appropriate isolation, patient-dedicated equipment, and, in some cases, private, negative pressure rooms. ◘ Table 37.11 provides details of isolation types with associated preventive measures and isolation recommendations for selected infectious organisms. Complete instructions are available on the CDC website ► https://www.cdc.gov/infectioncontrol/guidelines/isolation/.

37.8.3 Manage Devices Meticulously and Remove as Soon as Possible

Devices should not be routinely replaced since there is no evidence that this decreases the likelihood of nosocomial infections. Whenever a device is inserted, it should be done with the recommended sterility. Full sterility involves sterile gowns, sterile gloves, masks, caps, large sterile drapes that cover the patient completely, proper preparation of the skin with antiseptic solutions, limiting personnel in the room, and restarting/halting of the procedure if sterility is broken. Full sterility is recommended for central catheter insertions, PICC insertions, chest tube insertions, pericardiocentesis, paracentesis and ventricular/intracranial device placement.

Partial sterility (sterile gloves, mask, partial sterile drape, disinfectant solution) is acceptable for some procedures such as urinary catheter insertion, lumbar puncture, central line dressing changes, and peripheral arterial line insertion.

Table 37.11 Specific isolation recommendations

Action	Standard	Contact	Droplet	Airborne	Enteric
Single room	No	Yes or cohort	Yes or cohort	Yes	Yes
Negative pressure	No	No	No	Yes	No
Hand hygiene	Soap/water Antimicrobial soap/water ABHR	Antimicrobial soap ABHR for MDRO	Soap/water Antimicrobial soap/water ABHR	Soap/water Antimicrobial soap/water ABHR	Antimicrobial soap and warm water (not ABHR alone)
Gloves	When touching bodily fluids[a] or non-intact skin	Before touching patient or environment, remove before leaving room	When touching bodily fluids or non-intact skin	When touching bodily fluids or non-intact skin	Before touching patient or environment, remove before leaving room
Gown	When anticipating contact with bodily fluids	When entering the room, must dispose before leaving	When anticipating contact with bodily fluids	When anticipating contact with bodily fluids	When entering the room, must dispose before leaving
Mask +/– Eye protection	When anticipating contact/splashing of bodily fluids	When anticipating contact/splashing of bodily fluids	When entering the room, remove and dispose before exit by handling the loops	Particulate respirator applied before entering room, remove *after* exiting the room	When anticipating contact/splashing of bodily fluids
Common organisms	CMV, HIV, Hepatitis B/C, *Aspergillus*	MRSA, VRE, *E. coli*, HSV, lice, scabies, non-*C. difficile* diarrhea[b], HZV With cough and respiratory symptoms, use mask as well for adenovirus, enterovirus, RSV, MRSA	*B. pertussis*, influenza, mumps, rubella, Coxsackie, *Neisseria meningitidis*, bacterial meningitis[c], rhinovirus (children)	VZV, disseminated HZV, rubeola (measles) N-95 respirator for TB, SARS, avian influenza	*Clostridium difficile* (some institutions: rotavirus, norovirus)

Source: CDC (2019)

ABHR alcohol-based hand rinse, *MDRO* multidrug-resistant organisms, *CMV* cytomegalovirus, *HIV* human immunodeficiency virus, *MRSA* methicillin-resistant *Staphylococcus aureus*, *VRE* vancomycin-resistant *Enterococcus*, *HSV* herpes simplex virus: *HZV* herpes zoster virus (shingles), *RSV* respiratory syncytial virus, *VZV* varicella zoster virus (chicken pox), *TB Mycobacterium tuberculosis*, *SARS* severe acute respiratory syndrome

[a]Bodily fluids – patients' secretions, blood, excretions

[b]Non-*C. difficile* diarrhea – rotavirus, norovirus, hepatitis A, *Salmonella*, *Shigella*, *E. coli 0157H7*

[c]For the first 24 h after appropriate antibiotic coverage

Clean or aseptic technique involves clean, gloved hands and cleaning of device insertion site with appropriate antiseptic solutions when indicated. This can be used for peripheral intravenous catheter insertion, endotracheal/nasotracheal intubation and/or suctioning, and nasogastric tube placement.

Once any device has been inserted, manipulation of the device and entry into it should be minimized including line access and breaking into ventilator circuits for suctioning, bronchoscopy, or respiratory treatments. Meticulous and constant attention should be given to the appearance and proper functioning of devices such as reduction of accumulated ventilator moisture in tubing, impeded urinary catheter flow due to drain occlusion or full collection bags, central line site and dressing maintenance, and/or catheter occlusion. Devices should be removed as soon as possible balancing the need for the device with the risk of infection. Decisions about removal should be made *daily* and incorporated into routine patient work flow including rounds. When local or systemic symptoms of infection occur, a high index of suspicion for device infection should occur with cultures obtained from the device if possible.

37.8.4 Use Standard Criteria for Diagnosing Infections

Both under- and overdiagnosis of HAI should be avoided. Careful collection of culture specimens is imperative to avoid contaminated and confusing results. Standard criteria for identifying true infections should be followed, recognizing that judgments will be required in individual situations, especially in those where definitions include clinical, laboratory, and/or radiologic parameters. Full definitions of various nosocomial infections are available on the CDC website.

37.8.5 Use Antibiotics When Clearly Indicated

Bacterial resistance to antibiotics is increasing. Vancomycin-resistant *Enterococcus* and oxacillin-/methicillin-resistant *Staphylococcus aureus* are much more common than previously appreciated. The spectrum of resistance associated with *Escherichia coli*, particularly fluoroquinolone resistance, is increasing. NHSN data through 2014 indicated that 15 pathogen groups account for 87% of antibiotic resistance. Among HAI, *Escherichia coli* (15%), *Enterococcus* species, *Staphylococcus aureus* (12%), *Candida* species, *Klebsiella* species (8%), coagulase-negative staphylococci (8%), and *Enterococcus faecalis* (7%) are the most common. Device-associated HAI were more likely to have resistant organisms isolated compared to surgical site infections. Gastrointestinal surgeries accounted for 51% of surgical site infections followed by orthopedic surgeries accounting for 23%. Since increased resistance is likely related to overuse of antibiotics, prudent selection of antibiotics in suspected infection and use of narrow-spectrum antibiotics in identified infections, based on organism antibiotic sensitivity panels, are critical. Both the individual patient history of resistant organisms and local and unit incidence rates should influence antibiotic choice. Prophylactic antibiotics should be used only if evidence demonstrates a clear benefit (e.g., perioperative antibiotics). Toxicities of antibiotics (e.g., piperacillin-tazobactam and acute kidney injury) should also be considered with dosing adjusted for renal or hepatic dysfunction and serum levels obtained when appropriate.

37.8.6 Minimize Exposure of Patients to Visitors/Staff with Transmittable Infections

Respiratory syncytial virus, enteroviruses, and *Staphylococcus aureus* have all been reported to be transmitted to patients in a healthcare setting. It is likely that other viruses are spread as well, but there are little data to specifically support isolation practices. If staff and visitors have a transmittable illness, especially respiratory or gastrointestinal, appropriate precautions should be taken to shield patients. Ideally, infected staff and visitors should not have any direct patient contact if possible. If contact is unavoidable, exceptional attention to good handwashing and gloves should be utilized in all cases, and masks and gowns should be used based on symptoms.

37.9 Conclusion

HAIs contribute significantly to the morbidity and mortality of PICU patients. Since care for critically ill children necessitates invasive technology, meticulous attention to the prevention of device-related HAI remains essential. A multidisciplinary effort by physicians, nurses, respiratory therapists, environmental services, infection control specialists, device manufacturers, engineers, and unit architects can create an environment that prevents a patient's exposure to infectious agents carried by others or invasion by organisms with which the patient is colonized. The centuries-old adage "primum non nocere" continues to be relevant in this setting, and our attempts to decrease HAI in PICU patients is but one application of this wisdom.

Review Questions

1. The most common nosocomial infection in the pediatric intensive care unit is:
   A. Bloodstream infection
   B. Gastrointestinal infection
   C. Urinary tract infection
   D. Ventilator-associated pneumonia
   E. Wound infection

2. Which of the following is the most reliable method for diagnosing a ventilator-associated pneumonia?
   A. Blind, non-bronchoscopic alveolar lavage culture
   B. Blind, non-bronchoscopic alveolar lavage culture and protected brush specimen
   C. Blind, non-bronchoscopic protected specimen brush culture
   D. Chest X-ray
   E. Endotracheal aspirate culture

3. Most pediatric ventilator-associated pneumonias are caused by:
   A. Coinfection with Gram-negative and Gram-positive bacteria
   B. Gram-negative bacteria
   C. Gram-positive bacteria
   D. Viruses
   E. Yeast

4. Which of the following is NOT recommended to prevent nosocomial infection in the pediatric intensive care unit?
   A. Elevating the head of the bed to at least 30 degrees
   B. Removing vascular lines, catheters, and tubes as soon as possible

C. Replacing central catheters every 5–7 days by rewiring with a fresh catheter
D. Using cap, gown, mask, and sterile gloves when inserting central lines
E. Washing hands before and after patients

5. Which of the following is the most common pathogen associated with wound infections in pediatric cardiac surgery patients?
A. *Candida albicans*
B. *Coagulase-negative staphylococci*
C. *Group A Streptococcus*
D. *Pseudomonas aeruginosa*
E. *Staphylococcus aureus*

6. A 4-month-old male infant with trisomy 21 develops fever 5 days after repair of a complete atrioventricular septal defect. He required a prolonged cardiopulmonary bypass time and deep hypothermic circulatory arrest to complete the repair. He returned to the PICU postoperatively with an open chest that was closed 36 h later. He remains intubated and requires continued myocardial support with epinephrine and milrinone infusions. His current vital signs are temperature 39.5 °C, pulse 167 beats/min, blood pressure 90/56 mmHg, and oxygen saturation of 92% on 50% FiO_2. His white blood cell count is 13,000 cells/μL with no band forms. His wound appears clean and dry. He has both arterial and central venous access. The Foley catheter was removed on postoperative day 3. The most correct statement regarding this child's current status is:
A. Nosocomial infection is unlikely considering the normal white blood count. The fever is likely a postoperative phenomenon and he requires observation.
B. Nosocomial infection should be suspected. Bloodstream infection with *Staphylococcus aureus* is most likely.
C. Nosocomial infection should be suspected. Despite the clean appearance, a deep wound infection due to Gram-negative organisms is most likely.
D. Nosocomial infection should be suspected. The infant's age, complex repair, and need for an open chest are substantial risk factors for postoperative nosocomial infection.
E. Nosocomial infection should be suspected. The infant's underlying trisomy 21 is the greatest risk factor for postoperative nosocomial infection.

7. A 9-year-old female sustained severe second- and third-degree burns on her anterior abdomen, pelvis, and thighs after a pot of boiling water spilled onto her. She is intubated and has an internal jugular central venous catheter and a urinary catheter in place. The most correct statement regarding her potential for nosocomial infection is which of the following?
A. She has a risk for nosocomial infection that is similar to other critically ill children with similar invasive devices.
B. She has a substantial increased risk for nosocomial infection. Bloodstream infections with enteric organisms are the most common nosocomial infection in this population.
C. She has a substantial increased risk for nosocomial infection. She requires prophylactic broad-spectrum antibiotics for 7–10 days.
D. She has a substantial increased risk for nosocomial infection. The highest device-related incidence of nosocomial infections in this population is ventilator-associated pneumonia and urinary tract infection.
E. She has a substantial increased risk for nosocomial infection. Ventilator-associated pneumonia and wound infections are common, whereas urinary tract infection is uncommon in this population.

Answers

1. C
2. B
3. B
4. C
5. E
6. D
7. D

Suggested Readings

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Hematology

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Disseminated Intravascular Coagulation

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Learning Objectives

- The reader should understand the pathophysiologic basis of disseminated intravascular coagulation (DIC) and detail the common precipitating causes of this condition.
- The reader should be able to apply an understanding of DIC pathophysiology to clinical trials of therapeutic interventions.
- The reader should be able to list a differential diagnosis of conditions causing DIC in the critically ill child.

38.1 Introduction

Disseminated intravascular coagulation (DIC) has been defined by the Scientific and Standardized Committee of the International Society on Thrombosis and Haemostasis (ISTH) "as an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction." It is never an independent clinical condition, but always secondary to an underlying disorder; a wide variety of conditions may result in DIC (▶ Box 38.1). The microvascular thrombosis associated with DIC is the result of enhanced fibrin formation and/or decreased fibrin removal as well as endothelial cell injury.

In general, coagulopathy is a marker of serious illness, but its clinical severity can vary. Pediatric intensive care practitioners recognize the increased morbidity and mortality that DIC causes to hospitalized patients. In adults, a population-based retrospective cohort study of critically ill patients with DIC from 2004 to 2010 revealed a decreasing incidence from 26.2% per 100,000 person-years (95% CI, 17.1–38.4) to 18.6% (95% CI, 10.6–37.9), and no difference in case fatality during the same period. In children, there are no population-based studies evaluating the incidence of DIC in severely ill patients. To date, prevalences of DIC in the pediatric intensive care setting range from 1% to as high as 60%. This wide prevalence range can be explained by the differences in study designs, the diagnostic methods used to identify DIC, and patient populations. Importantly, the development of DIC effects outcome in the pediatric intensive care unit (PICU), with higher DIC scores (see below) associated with increased mortality for children with sepsis and septic shock.

Box 38.1 Clinical Conditions That May Be Associated With Disseminated Intravascular Coagulation

- Sepsis
- Trauma (e.g., polytrauma, neurotrauma, and fat embolism)
- Organ destruction (e.g., severe pancreatitis)
- Malignancy
  - Solid tumors
  - Myeloproliferative/lymphoproliferative malignancies
- Obstetrical calamities
  - Amniotic fluid embolism
  - Abruptio placentae
- Vascular anomalies
  - Vascular tumors (kaposiform hemangioendothelioma) complicated by Kasabach-Merritt phenomenon
  - Vascular malformations (simple [venous or lymphatic] or combined [veno-lymphatic])

- Severe hepatic failure
- Severe toxic or immunological reactions
  - Snake bites
  - Recreational drugs
  - Transfusion reactions
  - Transplant rejection

Adapted from Levi et al. (2004)

38.2 Pathophysiology

DIC appears to be precipitated by one of the two general pathophysiologic processes: a systemic inflammatory response with activation of the cytokine network and subsequent activation of coagulation (e.g., sepsis), and/or the release or exposure of procoagulant materials into the bloodstream (e.g., cancer).

Despite the wide variety of precipitating conditions (▶ Box 38.1), the syndrome appears to result from one of the two general pathophysiologic processes. It may be induced by either a systemic inflammatory response with activation of the cytokine network and subsequent activation of coagulation (e.g., sepsis), and/or the release or exposure of procoagulant materials into the bloodstream (e.g., cancer). However, even among these two broad pathophysiologic categories, burgeoning data suggest that differences may exist based on the underlying precipitant of the DIC. For example, trauma associated DIC appears to be characterized by excess, albeit transient, fibrinolysis seemingly in response to substantial thrombosis. In contrast, sepsis-induced DIC occurs with activation of the coagulation cascade and inhibition of fibrinolysis. Furthermore, the specific mechanisms that drive the DIC process, particularly for inflammatory-mediated DIC, are becoming increasingly clear (▶ Box 38.2).

The principal initiator of inflammation-induced thrombin generation is tissue factor.

To begin to understand this complex process, it is first necessary to recognize that the principal initiator of inflammation-induced thrombin generation is tissue factor. Tissue factor, an integral membrane glycoprotein, is normally expressed on cells extrinsic to the vascular compartment, but its expression can be induced in monocytes, and perhaps in endothelial cells, by inflammatory mediators. In severe sepsis, pathogens and their components stimulate monocytes to express tissue factor, release cytokines, and release extracellular vesicles which activate platelets and neutrophils. Activated neutrophils and extracellular vesicles also express tissue factor.

In addition to the augmented expression of tissue factor, sepsis fuels DIC via other mechanisms. For example, proinflammatory damage-associated molecular patterns (DAMPs) are now believed to contribute to the pathophysiology of DIC. Sepsis-induced cellular injury results in the release of these DAMPs, which include cell-free DNA, histones and high mobility group box-1 (HMGB1) protein, into the tissues and the circulation that contribute to DIC via activation of coagulation, platelet aggregation and inhibition of fibrinolysis. Neutrophils further this process by releasing their neutrophil extracellular traps (NETs) composed of procoagulant DNA, histones, and other DAMPs. These NETs are fibers consisting primarily of cell-free DNA and granular enzymes that trap pathogens and promote their destruction. The NETs foster DIC by stimulating the release of extracellular tissue factor, activating factor XII and cleaving serine protease inhibitors. Finally, sepsis-induced injury of endothelial cells results in disruption of the glycocalyx and expression of ultra-large von Willebrand factor promoting a procoagulant state within the vasculature (◘ Fig. 38.1).

More specifically, tissue factor expressed at the cell surface interacts with factor VII ultimately forming a tissue factor–factor VIIa complex (extrinsic factor Xase) that catalyzes the activation of factors IX and X (◘ Fig. 38.2). The initial factor Xa produced catalyzes the conversion of small amounts of

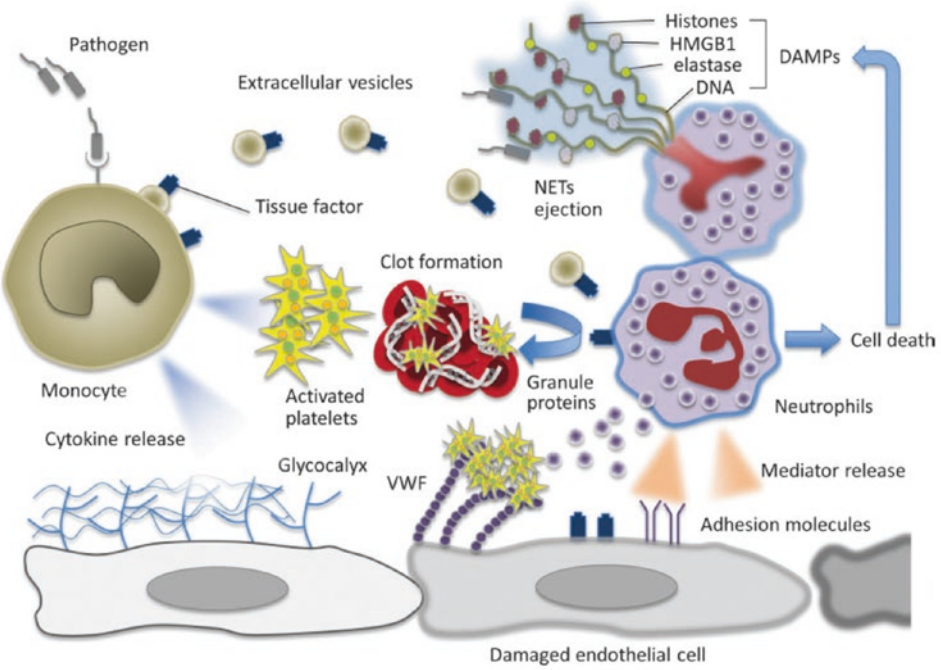

Fig. 38.1 Complex mechanisms for the activation of coagulation during sepsis. Pathogens and their components stimulate monocytes through specific receptors on the cell surface. Activated monocytes release cytokines, chemokines, and several chemical mediators that activate platelets, neutrophils, and endothelial cells. Monocytes and other cells release extracellular vesicles that express procoagulant tissue factor and phosphatidylserine on their surfaces. Damaged endothelial cells change their anticoagulant properties to procoagulant through the disruption of the glycocalyx and the expression of ultralarge von Willebrand factor (VWF). Neutrophils play major roles in the activation of coagulation by expressing tissue factor and releasing granule proteins and mediators. Neutrophils also activate coagulation by expelling neutrophil extracellular traps (NETs), composed of procoagulant DNA, histones, and other damage-associated molecular patterns (DAMPs). HMGB1 is high mobility group box-1 protein. (Copied with permission from: Iba T, Levi M, Levy JH. Sepsis-Induced Coagulopathy and Disseminated Intravascular Coagulation. Semin Thromb Hemost. 2020;46:90)

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Thrombin is critical to the development of DIC. In addition to catalyzing the formation of fibrin, it is essential in regulating physiologic anticoagulant and fibrinolytic pathways and serves as a potent activator of platelets.

Defective function of the three major endogenous anticoagulation systems results in increased availability of thrombin and contributes to the pathophysiology of DIC.

prothrombin to thrombin in a highly inefficient manner. However, the formation of this small amount of thrombin, known as the initiation phase, is essential as it accelerates the process by activating platelets, factor V, and factor VIII. Once factor VIIIa is formed, it combines with factor IXa (generated by the tissue factor–factor VIIa complex) on the activated platelet membrane to form the "intrinsic factor Xase" which becomes the major activator of factor X. The factor IXa-factor VIIIa complex is 10^5–10^6 fold more active than factor IXa alone, and several fold more efficient than the tissue factor–factor VIIa complex, in activating factor X. The activated factor X, in conjunction with factor Va, forms the "prothrombinase" complex that converts prothrombin to thrombin being 300,000 fold more active than factor Xa alone. Thrombin, in turn, cleaves fibrinogen into fibrin monomers that are subsequently cross-linked into stable polymerized fibrin.

Clearly, thrombin is critical to the development of DIC. In addition to catalyzing the formation of fibrin, it is essential in regulating physiologic anticoagulant and fibrinolytic pathways and serves as a potent activator of platelets. Activated platelets form the essential phospholipid surface on which the assembly of these complexes of activated coagulation factors occurs, thereby accelerating the coagulation process. Moreover, cytokines also interact with endothelial cells at areas of injury or ischemia increasing the expression of procoagulants by the endothelial cells. This change ultimately results in a switch of the endothelial layer from an anticoagulant to a procoagulant surface that assists with local promotion of clotting.

In addition to enhanced tissue factor-mediated thrombin formation, defective function of the three major endogenous natural anticoagulation systems

may also result in increased availability of thrombin and contribute to the pathophysiology of DIC (Fig. 38.2). First, antithrombin, which combines with thrombin to form thrombin–antithrombin complexes, and thereby serves as the principal inhibitor of thrombin, is found in very low levels during DIC. These decreased levels of antithrombin are secondary to increased consumption, decreased synthesis, and degradation by elastases from activated neutrophils. Additionally, antithrombin function is impaired because of decreased availability of glycosaminoglycan, a physiologic co-factor of antithrombin, on the dysfunctional endothelial cells. The finding that decreased levels of antithrombin precede clinical findings of sepsis supports a pathogenic role of these decreased levels. Second, there is decreased function of the protein C pathway as a result of both decreased levels and down-regulation of thrombomodulin. The decreased levels are secondary to increased consumption and decreased synthesis. Proinflammatory cytokines such as TNF-alpha and IL-1B inhibit protein C activity by down-regulating thrombomodulin expression on endothelial cells. Thrombomodulin is an endothelial surface protein that reduces blood coagulation by converting thrombin to an anticoagulant enzyme which increases protein C activation a thousand-fold. The third major endogenous anticoagulant, tissue factor pathway inhibitor (TFPI), normally functions to inhibit thrombin formation by inactivating the tissue factor–factor VIIa complex by forming a quaternary structure with it and factor Xa. The role of TFPI in the pathogenesis of DIC, however, is not completely clear. Although clinical studies have failed to demonstrate decreased levels of TFPI in the majority of patients with DIC, administration of recombinant TFPI has been found to block inflammation-induced thrombin generation in humans. Moreover, although endogenous concentrations of TFPI are seemingly insufficient to regulate the deranged coagulation process during inflammatory conditions, pharmacological doses of TFPI have been reported to decrease mortality during systemic inflammation suggesting that high concentrations of TFPI are capable of modulating tissue factor-mediated coagulation.

Box 38.2 Primary Pathophysiologic Mechanisms Contributing to Inflammation-Induced Disseminated Intravascular Coagulation

- Enhanced tissue factor-mediated thrombin formation
  - Proinflammatory cytokines
  - Neutrophils
  - Extracellular vesicles
  - Neutrophil extracellular traps
- Defective function of the three major endogenous anticoagulation systems
  - Low concentrations and impaired function of antithrombin
  - Decreased function of the protein C pathway (decreased protein C levels and down-regulation of thrombomodulin)
  - Seemingly insufficient endogenous levels of tissue factor pathway inhibitor to regulate the deranged coagulation process during inflammatory conditions
- Inhibition of fibrinolysis primarily as a result of sustained increased levels of plasminogen activator inhibitor-1

In addition to augmented thrombin, and subsequently, fibrin formation, impaired fibrin elimination also contributes to the pathogenesis of DIC (Fig. 38.2). In fact, studies suggest that at the time of maximal coagulation activation in DIC, fibrinolysis is largely inhibited. Endothelial cells again play a pivotal role as the major fibrinolytic activators and inhibitors are produced and

Inhibition of fibrinolysis, which occurs primarily as a result of increased levels of plasminogen activator inhibitor-1 (PAI-1), also contributes to the pathogenesis of DIC.

stored in these cells. After an initial, brief increase in fibrinolytic activation, inhibition of fibrinolysis occurs primarily as a result of sustained increased levels of plasminogen activator inhibitor-1 (PAI-1). TNF-alpha and IL-1 stimulate PAI-1 synthesis and release, and decrease plasminogen activator synthesis. In addition to endothelial cells, PAI-1 may also be released from activated platelets. Further, there are data to suggest that fibrinolysis may also be suppressed by thrombin-activatable fibrinolytic inhibitor (TAFI) although the role of this pathway in DIC has not been well established.

Activation of coagulation has been found to contribute to proinflammatory responses. The binding of thrombin to specific cell receptors known as protease-activated receptors (PARs) appears to be the primary mechanism by which this proinflammatory response is induced.

In addition to inflammatory processes stimulating the coagulation cascade, activation of coagulation has been found to contribute to proinflammatory responses. For example, factor Xa, thrombin, fibrin, and the tissue factor–factor VIIa complex have all been found to elicit proinflammatory processes. More specifically, the binding of thrombin to specific cell receptors known as protease-activated receptors (PARs) appears to be the primary mechanism by which this proinflammatory response is induced. These PARs are located in the vasculature on endothelial cells, platelets, mononuclear cells, fibroblasts and smooth muscle cells. Four PARs are known in humans. Human PAR1, PAR3, and PAR4 can be activated by thrombin, while PAR2 is activated by the tissue-factor-factor VIIa complex and factor Xa, but not by thrombin. The effect of these coagulation proteins on inflammation is supported by the clinical finding that infusion of recombinant factor VIIa in healthy human subjects results in small, but significant increases in the concentrations of IL-6 and IL-8, a response that is absent when volunteers are pretreated with an inhibitor of tissue factor–factor VIIa. In addition to the effect of these coagulation proteins, the three endogenous anticoagulant pathways can also influence inflammation. For example, activated protein C has been found to inhibit TNF-alpha release from monocytes both *in vitro* and *in vivo* and to block leukocyte adhesion *in vivo*. It has also been demonstrated to inhibit endotoxin-induced production of IL-1B, IL-6, and IL-8 in cultured monocytes and macrophages. Furthermore, inhibition of the protein C pathway increases cytokine elaboration, endothelial cell injury and leukocyte extravasation in response to endotoxin, processes that are decreased by the infusion of activated protein C. Moreover, infusion of recombinant activated protein C accelerated the decrease of IL-6 levels in humans with severe sepsis. In addition, recent laboratory experiments demonstrate common pathways in which coagulation directly relates to innate immunity against pathogens and microorganisms, contributing to the inflammation-coagulation interface. Briefly, infectious processes are responsible for recruiting cells and proteins that facilitate both immunity and coagulation (e.g., neutrophil extracellular traps [NETs]). Likewise, thrombomodulin, the protein that binds to thrombin with subsequent activation of protein C, is also involved in the negative regulatory effect of high mobility group box-1 (HMGB1), a cytokine storm elicitor, contributing to the direct inactivation of complement C3b, and the indirect inactivation of complements C5a and C3a. Clearly, inflammatory responses are influenced by coagulation processes and this remains an area of much interest and research.

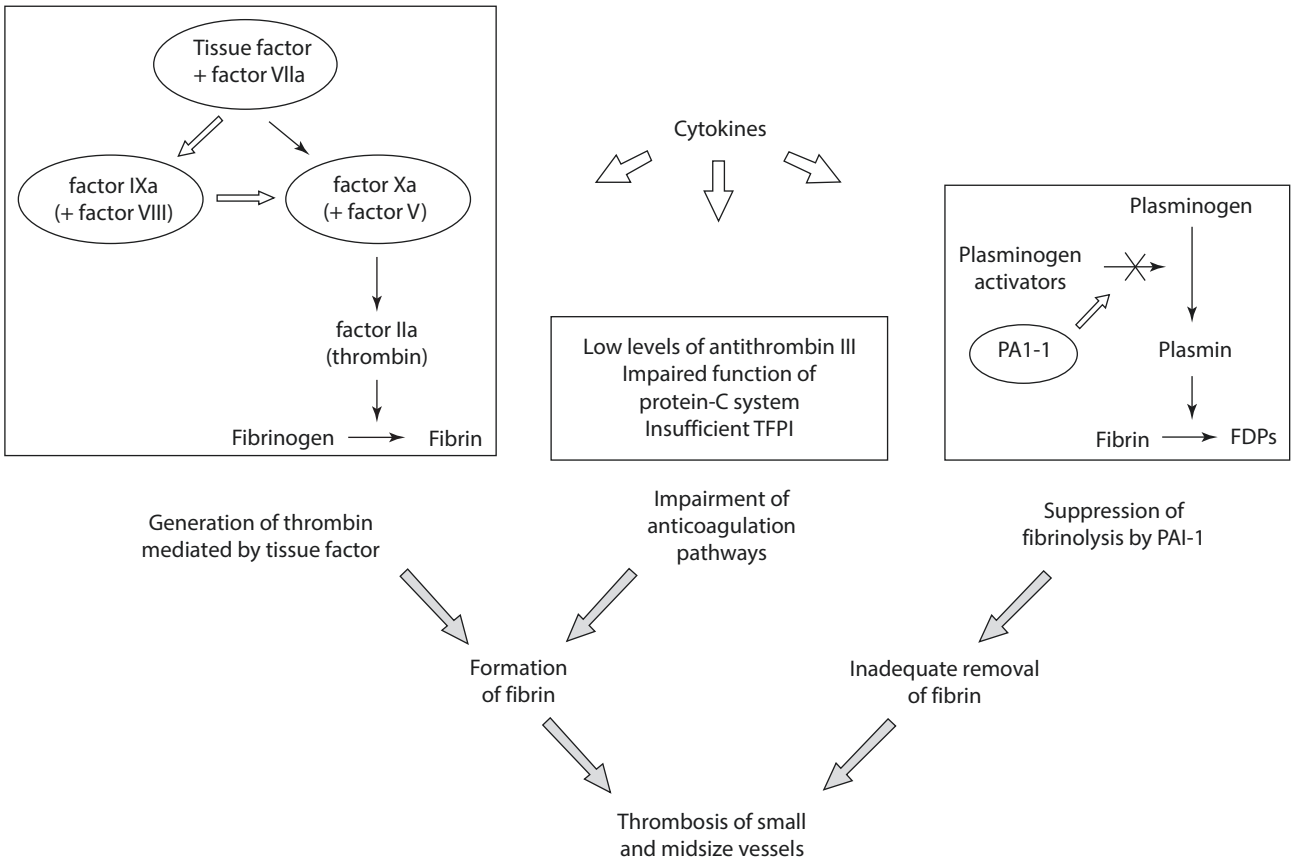

Fig. 38.2 Pathogenic pathways involved in disseminated intravascular coagulation. In patients with disseminated intravascular coagulation, fibrin is formed as a result of the generation of thrombin mediated by tissue factor. Tissue factor, expressed on the surface of activated mononuclear cells and endothelial cells, binds and activates factor VII. The complex of tissue factor and factor VIIa can activate factor X directly (*black arrows*) or indirectly (*white arrows*) by means of activated factor IX and factor VIII (top left box). Activated factor X, in combination with factor V, can convert prothrombin (factor II) to thrombin (factor IIa) which drives the conversion of fibrinogen into fibrin (top left box). Simultaneously, all three physiologic means of anticoagulation–antithrombin, protein C system (thrombin, thrombomodulin, protein C, and protein S) and tissue factor–pathway inhibitor (*TFPI*) – are impaired (upper middle box). The resulting intravascular formation of fibrin is not balanced by adequate removal of fibrin because endogenous fibrinolysis is suppressed by high plasma levels of plasminogen-activator inhibitor type 1 (*PAI-1*) (top right box). The high levels of PAI-1 inhibit plasminogen-activator activity and consequently reduce the rate of plasmin formation. The combination of increased formation and inadequate removal of fibrin results in disseminated intravascular thrombosis. *FDP* denotes fibrin-degradation products (Adapted from Levi and ten Cate (1999))

38.3 Clinical Aspects

The clinical spectrum of DIC can be quite diverse ranging from a subclinical decrease in the platelet count or prolongation in the laboratory coagulation screening times to fulminant DIC with widespread microvascular thrombosis, multisystem organ dysfunction and profuse bleeding. As stated above, DIC is always secondary to an underlying disorder and there are a wide variety of conditions that may result in DIC (▶ Box 38.1).

In pediatrics, sepsis is one of the most common etiologies of DIC. In bacterial sepsis, there is no difference in the incidence of DIC between gram negative and gram positive organisms. In both cases, DIC is triggered by either specific components from the microorganism cell membrane (lipopolyssacharide or endotoxin) or bacterial exotoxins (e.g., Staphylococcal alpha toxin).

The clinical spectrum of DIC can be quite diverse ranging from a subclinical decrease in the platelet count or prolongation in the laboratory coagulation screening times to fulminant DIC with widespread microvascular thrombosis, multisystem organ dysfunction and profuse bleeding.

In addition to sepsis, DIC is commonly found in severe trauma patients and is closely linked to the development of multiple organ dysfunction syndrome and worse outcomes. Trauma-induced coagulopathy (TIC) is a syndrome characterized by nonsurgical bleeding from mucosal, serosal and wound surfaces, secondary to trauma. A combination of factors may contribute to triggering DIC in severe trauma; clearly, activation of the cytokine network in a manner similar to sepsis is an established factor. Trauma associated DIC has a strong fibrinolytic component that has been considered the primary pathophysiology of patients whose hemostasis is deranged. Traumatic shock-induced tissue hypoperfusion causes tissue-type plasminogen activator (t-PA) release from endothelial Weibel–Palade bodies, leading to systemic fibrin(ogen)olysis in addition to DIC-induced secondary fibrinolysis. Conversely, the levels of plasminogen activator inhibitor-1 (PAI-1) are almost identical in patients with and without DIC, generating an imbalance that favors fibrinolysis.

Trauma associated DIC has a strong fibrinolytic component that has been considered the primary pathophysiology of patients whose hemostasis is deranged.

DIC is also common among patients with cancer. In children, laboratory evidence of DIC has been reported in 3% of untreated patients with acute lymphocytic leukemia and in nearly 14% of those with acute myelocytic leukemia. Children with acute promyelocytic leukemia (APL) appear to be at increased risk. DIC has also been reported among children with neuroblastoma and other solid tumors usually in the setting of extensive disease. The pathophysiology of DIC in cancer is less well established although expression of high levels of tissue factor and cancer procoagulant, hyperfibrinolysis in the setting of activated coagulation (APL), and the release of cytokines that enhance the prothrombotic potential, adhesive properties and permeability of the vascular endothelium have all been suggested. DIC has also recently been reported in patients with severe cytokine release syndrome (CRS) following chimeric antigen receptor (CAR)-T cell therapy. The occurrence of DIC in association with severe CRS portends a poor prognosis and is closely related to nonrelapse mortality during the acute toxicity period.

Additionally, vascular anomalies, classified by the International Society for the Study of Vascular Anomalies (ISSVA) as vascular tumors (e.g., kaposiform hemangioendothelioma) or vascular malformations (e.g., simple or combined vascular malformations) may lead to local activation of coagulation with systemic implications on hemostasis. This phenomenon can lead to an imbalance of systemic coagulation with subsequent consumption of platelets (i.e., Kasabach-Merritt phenomenon [KMP] in vascular tumors) and coagulation factors (i.e., localized intravascular coagulation [LIC] in vascular malformations).

38.4 Diagnosis

The diagnosis of DIC cannot be established on the basis of a single laboratory test, but it requires assessment of the entire clinical picture. The ISTH published a 5-step scoring algorithm to provide a practical diagnostic approach and a set of criteria for the diagnosis of DIC. To begin, and important to note, the presence of an underlying disorder known to be associated with DIC is a *conditio sine qua non* for the use of the algorithm. If such a condition does not exist, the algorithm should not be used. To continue, the scoring system requires assessment of simple, global coagulation tests that are routinely available in almost all hospitals, and provides a score for each based on the degree of derangement (■ Fig. 38.3). A total score of ≥5 is considered compatible with a diagnosis of overt DIC and has been associated with increased mortality in a prospective study.

The diagnosis of DIC cannot be established on the basis of a single laboratory test, but it requires assessment of the entire clinical picture. The ISTH has published a scoring algorithm to provide a practical diagnostic approach, which is used only if an underlying disorder associated with DIC is present.

Recently, the concept of sepsis-induced coagulopathy (SIC) has been suggested as a novel category to rapidly identify patients at risk for DIC. The

Risk assessment: Only use the scoring system if the patient has an underlying disorder known to be associated with overt DIC.

SCORING COMPONENTS

Platelet Count:Count: _____

- > 100K/μL = 0 points
- > 50K/μL –99K/μL = 1 points
- < 50K/μL = 2 points

Elevated Fibrin-related Markers: _____
(e.g. soluble fibrin monomers, fibrin degradation products)

- No increase = 0 points
- Moderate increase = 2 points
- Strong increase = 3 points

Prolonged Prothrombin Time: _____

- < 3 seconds = 0 points
- > 3 and < 6 seconds = 1 points
- > 6 seconds = 2 points

Fibrinogen Level: _____

- > 100 mg/dL = 0 points
- < 100 mg/dL = 1 points

TOTAL: _____

Fig. 38.3 The International Society on Thrombosis and Haemostasis (ISTH) Scientific Subcommittee on Disseminated Intravascular Coagulation Scoring System for Overt DIC. Algorithm for the diagnosis of overt disseminated intravascular coagulation (Adapted from Taylor et al. (2001))

ISTH DIC-Scientific and Standardized Committee proposed a diagnostic score for SIC among adults consisting of only three elements: the platelet count, the prothrombin time INR (International Normalized Ratio) and the sequential organ failure assessment (SOFA) score (Fig. 38.4). The score has subsequently been validated and compared to the standard ISTH diagnostic score for overt DIC. Studies of this novel scoring system in children are needed.

In addition, several molecular markers for the activation of coagulation or fibrin formation exist that are sensitive markers of DIC. However, their utility is limited because they lack specificity and are not readily available. Tests that are likely to be routinely available include tests for fibrin degradation products (FDPs) and D-dimers. D-dimers are specific degradation products that can only result from the digestion of cross-linked fibrin (Fig. 38.5). These tests are useful in that they are sensitive markers for DIC; thus, a normal D-dimer has a high negative predictive value for DIC. However, FDP and D-dimer levels also lack specificity. Fibrinogen levels have been suggested as a useful tool for the diagnosis of DIC. However, because fibrinogen acts as an acute-phase reactant, the levels can remain within the normal range for a long time despite active DIC, making it a less sensitive test. Serial monitoring of fibrinogen levels, as well as these other tests, is more useful than a single result in establishing the diagnosis of DIC. Another method, the waveform aPTT, has been found to be both a sensitive and specific detector of DIC in adults. This test analyzes the waveform produced by changes in light transmittance upon re-calcification of citrated plasma displayed by an automated laboratory machine while measuring the aPTT. In contrast to the normal sigmoid-shaped aPTT waveform, a biphasic waveform identified DIC in a study of 1470 samples with 98% sensi-

The waveform aPTT has recently been found to be both a sensitive and specific detector of DIC.

	0 Point	1 Point	2 Points	Score
Prothrombin time (INR)	≤1.2	> 1.2 to 1.4	> 1.4	
Platelet Count	≥ 150K/μL	< 150 to 100 K/μL	< 100 K/μL	
Four Item SOFA	0	1	≥2	
TOTAL				

Fig. 38.4 Algorithm for the diagnosis of sepsis-induced coagulopathy. (Diagnosed as sepsis-induced coagulopathy when the total score is 4 or more with the total score of prothrombin time and platelet count greater than 2. The total SOFA is the sum of the four items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, and renal SOFA). *INR* – international normalization ratio; *SOFA* – sequential organ failure assessment. (Adapted from Iba et al. (2017))

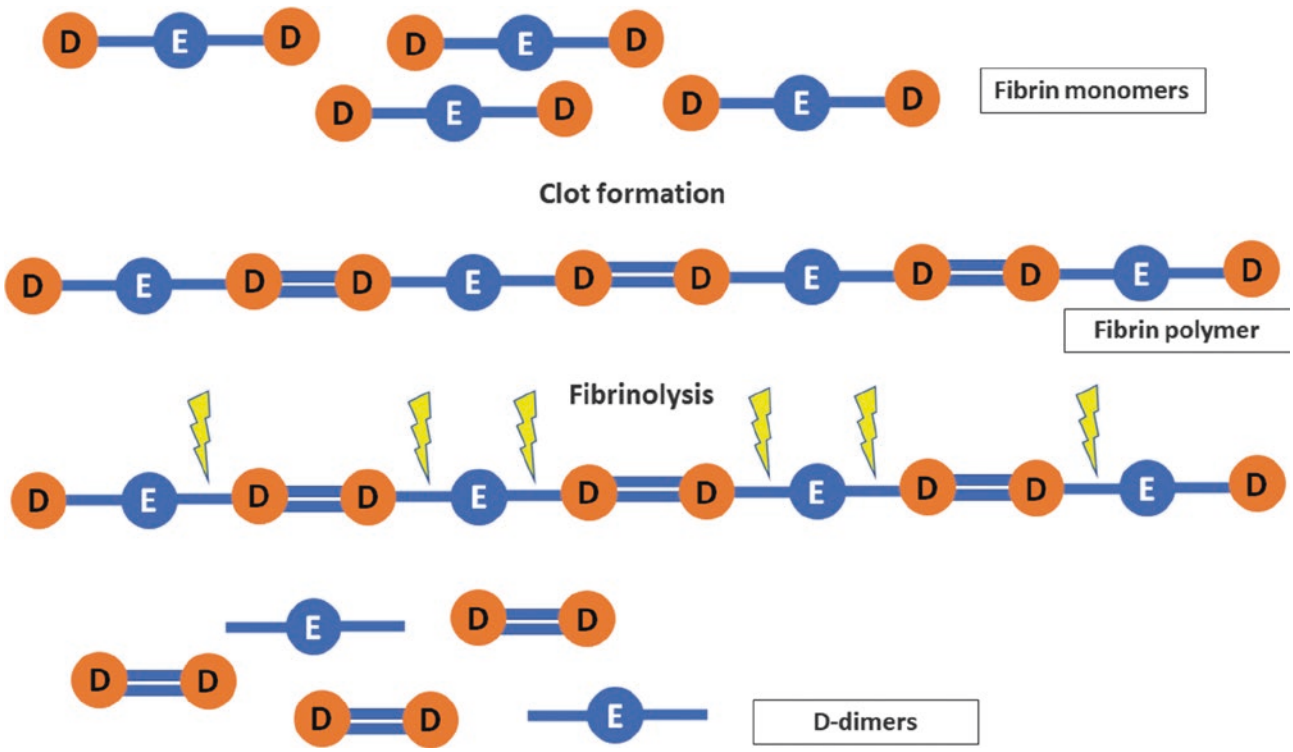

Fig. 38.5 Schematic representation of the formation of D-Dimers. The formation of cross-linked fibrin, an integral component of a clot, requires the conversion of fibrinogen to fibrin monomers, polymerization of the fibrin monomers to form fibrin polymers, and cross-linking of the fibrin polymers. As depicted in the schematic, the fibrin monomer consists of a central "E" component weakly attached via a single noncovalent bond to two "D" domains. When fibrin monomers bond to form fibrin polymers, a D domain from one monomer binds via two covalent bonds to the D domain of another monomer. This bond is stronger than the single noncovalent bond of the D arm to the E domain of the individual monomer. Thus, when fibrin polymers are degraded during fibrinolysis, D-dimers result given the stronger bond between D-D domains than between the D-E domains. Consequently, D-dimers can only arise when there is formation and degradation of cross-linked fibrin rendering them a useful tool in the diagnosis and monitoring of DIC

tivity, 98% specificity, and a positive predictive value of 74%. These changes seem to precede the more classical laboratory markers of DIC by approximately 24 h.

Point-of-care tests are also increasingly being used to assess disorders of coagulation among critically ill patients. For example, thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are being used with increased frequency in intensive care units as tools to assess global coagulation in whole blood samples. TEG, which was originally described in 1948, utilizes a pin suspended by a wire in a whole blood sample maintained at body temperature in a cuvette to analyze the physical properties of a forming blood clot. The wire is connected to a mechanical–electrical transducer. The elasticity, strength and dissolution of the clot changes the rotation of the pin. These changes are converted by the transducer into electrical signals that can be transformed into graphical and numerical outputs which are subsequently interpreted to provide insight into the state of various parameters of the coagulation process (◘ Fig. 38.6). ROTEM, or simply thromboelastometry (TEM), is a variation of this test in which a spinning pin is positioned in the cuvette and clotting is detected by reduced rotation of the pin. This technology allows for the assessment of the interaction among clotting factors and their inhibitors, anticoagulant medications and platelets during clot formation and subsequent dissolution (fibrinolysis). The role of TEG/TEM in diagnosing DIC is not well established, but the available data suggest it may be useful. TEG/TEM findings consistent with DIC have been found to correlate well with coagulation changes, organ dysfunction parameters and survival.

Although the early diagnosis of DIC is essential and holds the potential to improve outcomes, distinguishing DIC from other diseases and conditions may be challenging. For example, both DIC and liver disease are characterized by thrombocytopenia and low levels of coagulation factors. Moreover, DIC may occur concurrently with hepatic disease further complicating the diagnosis. However, clinical signs may help distinguish the two as findings such as ascites may suggest liver disease. In addition, parameters of the coagulation system may also help differentiate the two. In contrast to DIC, the thrombocytopenia of liver disease tends to be stable and markers of fibrinolysis (i.e., D-dimers) are only mildly increased. Additionally, because the alpha subunit of factor XIII is produced in megakaryocytes and white blood cells, the levels of factor XIII may remain relatively unchanged in liver disease (despite production of the beta subunit in the liver). In contrast, factor XIII levels are usually low in DIC. Similarly, factor VIII levels are normal in hepatic disease, but decreased in DIC.

Additionally, other conditions associated with endothelial cell injury and microvascular thrombosis (i.e., thrombotic microangiopathy) such as thrombotic thrombocytopenic purpura (TTP), Shiga toxin-mediated hemolytic uremic syndrome (HUS) and other "atypical" forms of HUS (aHUS) will be characterized by thrombocytopenia and schistocytes on peripheral smear as observed in DIC. However, these conditions are usually associated with normal laboratory coagulation screening times, and normal or only mildly elevated D-dimer levels. Establishing the correct diagnosis among these conditions is critical as the timely and appropriate institution of therapies for TTP, HUS, and aHUS can improve the outcomes including survival.

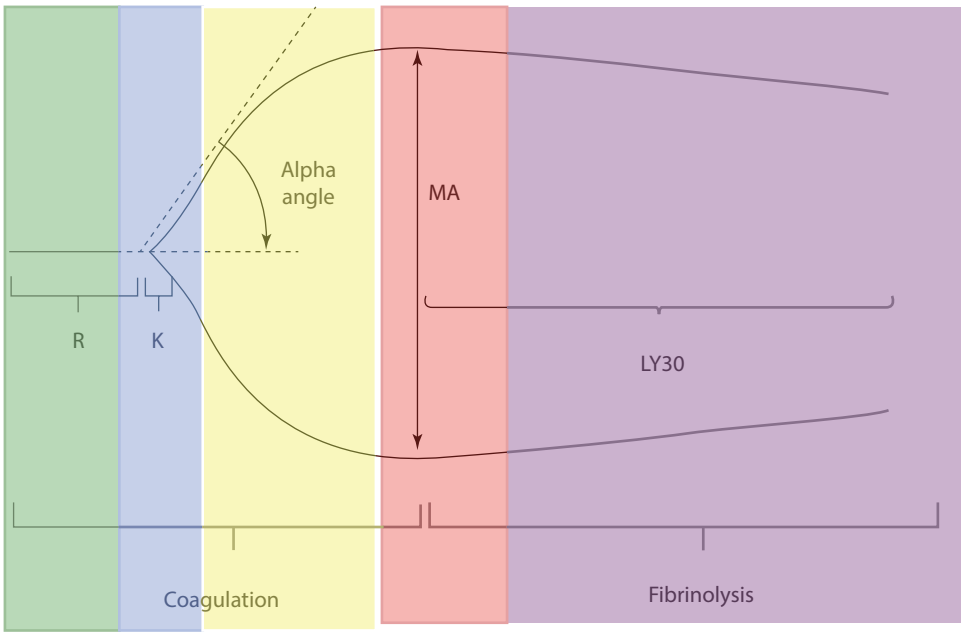

Fig. 38.6 Sample thromboelastogram. *Normal values vary by age. To apply this analysis to children, age specific norms willneed to be applied. (Figure Courtesy of Salim Rezaie. R.E.B.E.L. EM. ► https://rebelem.com/wp-content/uploads/2019/03/Thromboelastogram-TEG.png)

Thromboelastogram (TEG)

Components	Definition	Normal Values	Problem with...	Treatment
R Time	Time to start forming clot	5 - 10 minutes	Coagulation Factors	FFP
K Time	Time until clot reaches a fixed strength	1 - 3 minutes	Fibrinogen	Cryoprecipitate
Alpha angle	Speed of fibrin accumulation	53 - 72 degress	Fibrinogen	Cryoprecipitate
Maximum Amplitude (MA)	Highest vertical amplitude of the TEG	50 - 70 mm	Platelets	Platelets and/or DDAVP
Lysis at 30 Minutes (Ly30)	Percentage of amplitude reduction 30 minutes after maximum amplitude	0 -8Z	Excess Fibrinolysis	Tranexemic Acid and/or Aminocaproic Acid

* Normal values vary by age. To apply this analysis to children, age specific norms will need to be applied.

Hemolytic uremic syndrome (HUS) classically occurs as a triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure following a prodrome of bloody diarrhea.

A subset of patients develops HUS with no evidence of a Shiga toxin-producing infection, but rather with a mutation in a regulatory protein of the complement pathway.

In addition to microangiopathic hemolysis and thrombocytopenia, TTP, HUS and aHUS may be associated with organ dysfunction, and the distinction can be difficult. Classic HUS occurs as a triad of microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury. The most common form in children follows a prodrome of bloody diarrhea. This infectious form of HUS has been linked to a Shiga toxin-producing *E. coli 0157:H7* (STEC) or *Shigella dysenteriae* serotype 1 as well as a number of other infectious agents including *Streptococcus pneumoniae* and HIV. Noninfectious forms of HUS include hereditary conditions such as complement gene mutations, inborn errors of cobalamin C metabolism and diacylglycerol kinase epsilon gene mutations as well as acquired conditions associated with auto-antibody development towards complement factors. Although there is believed to be much overlap between HUS and TTP, renal dysfunction is a much more prominent feature of HUS than TTP.

TTP is characterized by a pentad of symptoms consisting of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal dysfunction, and neurologic findings although the complete pentad is observed in only a minority of patients. TTP tends to have a more insidious onset and a more prolonged course than HUS. Although the pathophysiology of TTP is incompletely understood, it is associated with a severe congenital or an acquired deficiency in the von Willebrand factor (vWF) protease (ADAMTS13) activity, which is responsible for cleaving vWF multimers into smaller, less thrombogenic multimers. The deficiency of this protease activity results in ultralarge and large vWF multimers that lead to excessive vWF-platelet binding causing microvascular thrombosis, consumptive thrombocytopenia and microangiopathic hemolysis.

Thrombotic thrombocytopenic purpura (TTP) is characterized by a pentad of symptoms consisting of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal dysfunction, and neurologic findings although the complete pentad is observed in only a minority of patients.

Atypical HUS (aHUS) is a group of diverse disorders that are characterized by defective complement regulation resulting in nonimmune hemolytic anemia, thrombocytopenia, and renal injury. The term aHUS is reserved for patients with HUS presentation without a co-existing disease. This is a diagnosis of exclusion, patients with suspected aHUS should undergo extensive workup to rule out *Streptococcus pneumoniae*–HUS, Influenza A/H1N1–HUS, TTP, STEC–HUS, Cobalamin C defect–HUS, and HUS with a co-existing disease (e.g., bone marrow transplantation, solid organ transplantation, cancer, autoimmune disorders, drugs, malignant hypertension, and HIV). Most commonly, patients with aHUS will have an identifiable genetic mutation in complement genes or anticomplement factor H (CFH) antibodies that lead to loss of endothelial and platelet protection from complement attack.

Many cases of TTP are associated with a congenital or an acquired deficiency in the von Willebrand factor (vWF) protease, ADAMTS13, which is responsible for cleaving vWF multimers into smaller, less thrombogenic multimers.

Treatment of infection-associated HUS is primarily supportive and dialysis may be required. Many other therapies have been employed with little controlled data. For atypical HUS, terminal complement blockade is the treatment of choice. More specifically, eculizumab, a monoclonal anti-C5 antibody that prevents the activation of the terminal complement pathway, is now the recommended therapy. As the immunity against *Neisseria meningitides* relies on the terminal complement complex, eculizumab increases the risk of meningococcal infections and patients should be educated accordingly. Plasma exchange may be used in those settings where eculizumab is not available. *For TTP, large volume plasma exchange should be implemented emergently*. Since children with TTP respond well to plasma exchange, the diagnosis of TTP should always be considered in the differential diagnosis of an atypical thrombocytopenia. Rituximab may be added if plasma exchange does not lead to rapid improvement. In addition, caplacizumab, a humanized, anti-von Willebrand factor immunoglobulin fragment that prevents the interaction between von Willebrand factor multimers and platelets has become the first FDA-approved treatment (in combination with plasma exchange and immunosuppressive therapy) for adults with acquired TTP. In a double blind, placebo controlled, multicenter, randomized phase 3 trial of 145 adults, caplacizumab in conjuction with plasma exchange was associated with a quicker normalization of the platelet count, and less mortality, recurrences, or thromboembolic events than plasma exchange alone.

Eculizumab, a monoclonal anti-C5 antibody that prevents the activation of the terminal complement pathway, is now the recommended therapy for atypical HUS.

Plasma exchange should be implemented emergently for TTP.

38.5 DIC Treatment

The treatment of DIC primarily involves aggressive treatment of the underlying condition and supportive care. Volume resuscitation, inotropic/vasopressor support, antimicrobials, and respiratory support must all be utilized as needed. Plasma and platelet substitution should be used in patients with active bleeding, those undergoing an invasive procedure, or those with a significant deple-

tion of these hemostatic factors. Routine replacement therapy based on laboratory results alone does not appear warranted. However, the recently published Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children suggested that children with worsening coagulation tests at high risk for disseminated intravascular coagulopathy *might* benefit from prophylactic plasma transfusions.

Anticoagulant therapy has been suggested as a potential treatment. Experimental data suggest that heparin therapy may be effective in blunting lipopolysaccharide-induced coagulation. In a randomized, double blind, placebo controlled trial of 30 healthy male volunteers who received a lipopolysaccharide infusion, both unfractionated heparin and low molecular weight heparin markedly decreased the activation of coagulation as compared to placebo. However, anticoagulant therapy with heparin has never been found to have a beneficial effect on clinically important outcomes in controlled trials of DIC and its use may be associated with an increased risk of bleeding. Some authors suggest that the use of therapeutic heparin is indicated in conditions with overt thromboembolism or with extensive fibrin deposition such as purpura fulminans or acral ischemia. If used, patients with DIC are usually given relatively low doses of heparin as a continuous infusion. Low-molecular-weight heparin may also be used as an alternative to unfractionated heparin.

With regard to vascular anomalies, vascular *tumors* associated with KMP were previously treated with vincristine, steroids and interferon-γ. More recently, sirolimus (an mTOR inhibitor) has revolutionized the care of these patients, leading to significant tumor size reduction and full correction of the severe thrombocytopenia that ensues during their rapid growth phase. Conversely, children with vascular *malformations* are at risk for localized intravascular coagulopathy (LIC). In those instances, acquired moderate hypofibrinogenemia and mild thrombocytopenia are noted in contrast to the severe thrombocytopenia found in patients with KMP. Patients whose LIC leads to severely affected fibrinogen levels are at risk for procedure-related and spontaneous intra- and extra-vascular malformation-related bleeding. Consequently, they can receive prophylactic courses of low molecular weight heparin particularly in the peri-procedural setting.

In addition to heparin, other anticoagulants have also been utilized to treat DIC. Given the pathophysiology of inflammation-mediated DIC, inhibitors of tissue factor appear to be logical therapeutic agents. In a randomized, double blind, placebo controlled, multicenter, phase 3 clinical trial of nearly 2000 septic adults, recombinant tissue factor inhibitor (tifacogin) failed to improve all cause 28-day mortality among patients with an INR $\geq$ 1.2. Patients treated with this medication failed to show improvement in any of the protocol-specified secondary endpoints and the use of the drug was associated with an increased risk of bleeding. Among treated patients with an INR < 1.2 in that trial, there was a strong trend towards improved survival although the increased bleeding risk persisted. Another potential therapy is the recombinant nematode anticoagulant protein c2 (rNAPc2) which is a potent inhibitor of the tissue factor–factor VIIa complex. Its mechanism of action is distinct from the tissue factor pathway inhibitor. In a phase 1 study in healthy, male volunteers, intravenous rNAPc2 was found to be safe and well tolerated. A single dose completely blocked endotoxin-induced thrombin generation without affecting the fibrinolytic response and attenuated the endotoxin-induced rise in IL-10, without affecting other cytokines. Blockade of IL-6 is another therapeutic consideration. Since IL-6 is postulated to be responsible for tissue factor expression in mononuclear and endothelial cells during severe sepsis, it is plau-

sible that IL-6 blockade may inhibit the activation of the coagulation cascade. Based on encouraging results in primates, a randomized, double blind, placebo controlled trial of a monoclonal anti-IL-6 antibody was conducted in healthy volunteers who received a lipopolysaccharide infusion. Unfortunately, the use of the IL-6 antagonist failed to decrease lipopolysaccharide-induced tissue factor mRNA transcription or plasma concentrations of any of the downstream coagulation factors. Finally, inactivated recombinant factor VIIa, which inhibits the binding of factor VIIa to tissue factor, has been reported to prevent tissue factor-induced thrombosis in animal models and to have potent antithrombotic effects in a perfusion chamber *ex vivo* human study. Its potential role in DIC requires further study.

Restoration of endogenous anticoagulant pathways is also being studied as potential therapy for DIC. Antithrombin is a serine protease inhibitor (i.e., serpin) and one of the most important physiologic inhibitors of coagulation, and patients with DIC almost invariably have an acquired deficiency. The administration of antithrombin concentrate has been extensively studied and utilized in the treatment of DIC for three decades. Several controlled clinical trials, mostly in patients with sepsis or with septic shock, found beneficial effects in terms of improvement in laboratory parameters, duration of DIC and even in organ function. However, in a randomized, double blind, placebo controlled, multicenter, phase 3 clinical trial in 2314 adult patients with severe sepsis (the KyberSept trial), high-dose antithrombin therapy had no effect on 28-day all cause mortality when administered within 6 h of the onset of sepsis, and, was associated with an increased risk of hemorrhage when administered with heparin. However, *post hoc* subgroup analyses suggested a treatment benefit of antithrombin in the subgroups of patients not receiving concomitant heparin, those at increased risk of mortality, and those with DIC. The finding of a treatment benefit with antithrombin in those not receiving concomitant heparin is particularly interesting given that the anticoagulant activity of antithrombin is increased severalfold when it binds to heparan sulfate on the endothelial glycocalyx attenuating glycocalyx injury. Available data regarding antithrombin therapy are limited in pediatric cases of DIC. However, in an open, randomized, controlled trial of 109 children diagnosed with acute lymphoblastic leukemia, 37 patients were treated with supraphysiologic doses of antithrombin to prevent thromboembolism. In this small study, antithrombin use was associated with a trend toward both efficacy and safety although the study was not sufficiently powered to address these issues.

Restoration of activated protein C represents another therapeutic target in inflammation-induced DIC since both the levels and activation of protein C are considerably diminished during severe sepsis. In a randomized, double blind, placebo controlled, multicenter trial (PROWESS) of 1690 adults with severe sepsis and at least one sepsis-induced organ dysfunction, the infusion of a recombinant form of human activated protein C (drotrecogin alfa) resulted in a highly significant reduction in 28-day all cause mortality. However, the use of recombinant activated protein C was associated with an increased risk of serious bleeding that approached statistical significance (3.5% vs. 2.0%, $P = 0.06$). Based on these encouraging results, and a study in 83 pediatric patients with severe sepsis demonstrating that the pharmacokinetics, pharmacodynamic effects, and safety profile of drotrecogin alfa (Xigris) in pediatric patients are similar to those in adults, a large, multicenter, randomized, double blind, placebo controlled, phase 3 study was initiated in children. Unfortunately, the trial was stopped secondary to futility after a planned interim analysis revealed that the therapy was highly unlikely to demonstrate an improvement over placebo in the primary endpoint of "Composite Time to Complete Organ

Failure Resolution" over 14 days. The Data Monitoring and Safety Committee also noted an increase in the rate of central nervous system hemorrhage in the treatment versus the placebo group. Over the infusion period (study days 0–6), four patients experienced an intracranial hemorrhage event among drotrecogin alfa-treated patients versus only one in the placebo group, with three of the four events in the drotrecogin alfa group occurring in patients aged 60 days or less. Mortality, the rate of serious adverse events, overall serious bleeding events, and major amputations appeared to be similar in the two groups. Based on these data, drotrecogin alfa cannot be recommended for use in pediatric severe sepsis. In addition, subsequent large scale, randomized, double blind, placebo controlled, multicenter study in adults failed to confirm the earlier encouraging findings of recombinant activated protein C.

Thrombomodulin supplementation has also been assessed as a therapeutic intervention for sepsis associated coagulopathy. In a randomized, double blind, placebo controlled, multinational, multicenter phase 3 trial (SCARLET trial) among 816 adults with sepsis-associated coagulopathy and concomitant cardiovascular and/or respiratory failure, the use of a recombinant human soluble thrombomodulin (ART-123) did not significantly reduce 28-day all cause mortality in critically ill patients with sepsis-associated coagulopathy. Interestingly, and similar to the KyberSept trial, there appeared to be a trend towards better outcomes with the use of recombinant thrombomodulin in those patients who did not receive concomitant heparin therapy. The severity of illness and the co-existence of DIC also appeared to have impacted outcomes.

In trauma patients, tranexamic acid (TXA), an antifibrinolytic agent, can reduce the risk of death in adult patients with bleeding and should be given as early as possible because any delay in administration after trauma reduces its efficacy and may be harmful. Similarly, early TXA administration (<3 hrs from injury onset) in adult patients with mild or moderate traumatic brain injury appears safe and efficacious, but not in patients with severe traumatic brain injury. Data regarding the use of TXA in pediatric trauma patients are lacking and more research is needed.

38.6 Conclusion

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Disseminated intravascular coagulation (DIC) is a syndrome characterized by systemic intravascular activation of coagulation resulting in widespread generation and deposition of fibrin in the circulation.

In conclusion, DIC is an acquired syndrome characterized by systemic intravascular activation of coagulation resulting in widespread generation and deposition of fibrin in the circulation. The resultant microvascular thrombosis appears to contribute to increased morbidity and mortality. The pathophysiologic basis of DIC is becoming progressively better understood thereby providing potential targets for therapeutic intervention. At the present time, treatment of DIC is focused on treating the underlying process activating the coagulation system. In addition, coagulation factors are replaced in those patients with clinical bleeding, those undergoing an invasive procedure or those having significant depletion of coagulation factors placing the patient at a high-risk of bleeding. The implementation of well designed clinical trials will continue to improve our understanding of the process and hopefully identify the most effective therapies.

Review Questions

1. Which of the following is the principal initiator of inflammation-induced thrombin generation?
   A. Antithrombin.
   B. Plasmin.
   C. Protein C.

D. Tissue factor.
E. Tissue factor pathway inhibitor.

2. Which of the following contributes to the pathophysiology of inflammation-induced disseminated intravascular coagulation (DIC)?
   A. Cytokine-induced expression of tissue factor resulting in enhanced tissue factor-mediated thrombin formation.
   B. Enhanced fibrinolysis primarily as the result of increased levels of plasminogen activator inhibitor-1 (PAI-1).
   C. Enhanced protein C function and activity as a result of increased synthesis and up-regulation of thrombomodulin.
   D. Increased levels and function of antithrombin as a result of decreased consumption, increased synthesis, and decreased neutrophil-mediated degradation.
   E. The more efficient activation of factor X by tissue factor-factor VIIa complex than by the factor IXa-factor VIIIa complex.

3. Which of the following is considered a *conditio sine qua non* for establishing the diagnosis of overt disseminated intravascular coagulation (DIC)?
   A. A fibrinogen level less than 100 mg/dL.
   B. A platelet count less than 50,000/μL.
   C. A prothrombin time in excess of 3 s.
   D. An elevated D-dimer level.
   E. The presence of an underlying disorder known to be associated with overt DIC.

4. The primary mechanism by which the coagulation cascade elicits a proinflammatory response is via the activation of which of the following receptors by thrombin and other coagulation proteins?
   A. Beta adrenergic receptors.
   B. Interleukin-1 receptors.
   C. Leukocyte adhesion receptors.
   D. Protease-activated receptors.
   E. Toll-like receptors.

5. Although the pathophysiology of thrombotic thrombocytopenic purpura (TTP) is incompletely understood, many cases are associated with a congenital or an acquired deficiency in which of the following proteins?
   A. ADAMTS13.
   B. Protein C.
   C. Tissue factor pathway inhibitor.
   D. Thrombopoietin.
   E. von Willebrand factor.

6. Thrombotic thrombocytopenic purpura (TTP) is characterized by which of the following pentad of symptoms?
   A. Diarrhea, fever, microangiopathic hemolytic anemia, neurologic abnormalities, and renal dysfunction.
   B. Diarrhea, fever, microangiopathic hemolytic anemia, neurologic abnormalities, and thrombocytopenic purpura.
   C. Diarrhea, fever, microangiopathic hemolytic anemia, renal dysfunction, and thrombocytopenic purpura.
   D. Diarrhea, fever, neurologic abnormalities, renal dysfunction, and thrombocytopenic purpura.
   E. Fever, microangiopathic hemolytic anemia, neurologic abnormalities, renal dysfunction, and thrombocytopenic purpura.

7. Which of the following treatments should be implemented for the acute treatment of thrombotic thrombocytopenic purpura (TTP)?
   A. Corticosteroids.
   B. Heparin infusion.
   C. Intravenous immunoglobulin.
   D. Macrolide antibiotics.
   E. Plasma exchange transfusion.

8. Hemolytic uremic syndrome (HUS) has been most commonly linked to which of the following?
   A. ADAMTS13 deficiency.
   B. Clostridium botulinum.
   C. Salmonella enteritidis infection.
   D. Shiga toxin-producing *E. Coli 0157:H7*.
   E. von Willebrand factor deficiency.

Answers

1. D
2. A
3. E
4. D
5. A
6. E
7. E
8. D

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Oncological Critical Care Considerations in Children

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Contents

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Learning Objectives

- To identify and understand the management of life-threatening clinical conditions associated with malignancies in children.
- To recognize and understand the management of life-threatening complications associated with the treatment of cancer in children.
- To understand common anticancer therapies and emerging immunotherapies including CAR T-cell therapy for the treatment of malignancies.
- To recognize and differentiate primary and secondary hemophagocytic lymphohistiocytosis (HLH).
- To understand the initial management of HLH.

39.1 Introduction

Pediatric oncological critical care is a rapidly evolving subspecialty within the critical care complex. Children with oncological disease are among the most vulnerable patients in the pediatric intensive care unit (PICU). These patients have higher rates of morbidity and mortality compared to other PICU patients. These patients frequently present with life-threatening conditions. Also, therapies to treat the underlying oncological conditions have systemic toxicities that can lead to multiorgan complications. Thorough knowledge of the toxic effects of various therapies including chemotherapy, radiotherapy, and immunotherapy is necessary to recognize, prevent and/or treat potential complications. The majority of these patients develop a prolonged immunocompromised state, which increases their risk of developing severe sepsis and septic shock with or without atypical opportunistic infections. Therefore, attention to the appropriateness of antimicrobial agents and adjunctive immunotherapy is required to timely and adequately treat these infections. Children undergoing hematopoietic cell transplantation (HCT) consist of a unique cohort among children with oncological disease with significant increase in the risk of mortality and morbidities. Children with HCT encounter various unique issues/complications during different phases (pre-engraftment, post-engraftment, after 100 days) of HCT including engraftment syndrome, sinusoidal obstruction syndrome, graft-versus-host disease, acute respiratory failure, acute kidney injury, and lymphoproliferative disease. These conditions are reviewed elsewhere in the textbook (▶ Chap. 40). Finally, children with primary or secondary hemophagocytic lymphohistiocytosis (HLH) can develop a hyperinflammatory cytokine release syndrome, which has features similar to severe sepsis. In this chapter, the readers will review the essential aspects of pediatric oncocritical care with focus on common life-threatening conditions and emphasis on critical care management.

39.2 Oncological Emergencies

39.2.1 Tumor Lysis Syndrome

Tumor lysis syndrome is a potentially life-threatening complication characterized by severe metabolic derangements including hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia.

Tumor lysis syndrome is a potentially life-threatening complication characterized by severe metabolic derangements including hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia. Malignancies at highest risk of tumor lysis are those with large, rapidly proliferating tumor burdens and high sensitivity to anticancer therapy (■ Table 39.1). Cairo and Bishop have published a grading system for tumor lysis syndrome based on clinical and laboratory variables (■ Table 39.2).

Table 39.1 Childhood malignancies associated with tumor lysis syndrome

Risk category	Malignancy
High	ALL with WBC > 100,000 cells/μL AML with WBC > 50,000 cells/μL Burkitt lymphoma (stage 3 or 4) Lymphoblastic lymphoma (stage 3 or 4) High-grade NHL High grade T-cell lymphoma
Medium	ALL with WBC 50,000–100,000 cells/μL AML with WBC 10,000–50,000 cells/μL Burkitt lymphoma (stage 1 or 2) Lymphoblastic lymphoma (stage 1 or 2) Low grade T-cell lymphoma Bulky germ cell tumor, sarcomas or other solid tumors
Low	Hodgkin lymphoma Chronic lymphoid leukemia Chronic myeloid leukemia Medulloblastoma Indolent sarcomas or other solid tumors

ALL acute lymphoid leukemia, *AML* acute myeloid leukemia, *WBC* white blood cell count, *NHL non-Hodgkin lymphoma*

The pathophysiological mechanism involves rapid lysis of tumor cells that leads to the release of large quantities of intracellular contents rich in potassium, phosphate, and purine nucleic acids. The release of potassium and phosphate into the bloodstream results in hyperkalemia and hyperphosphatemia. The ionized calcium in blood quickly binds to the excess phosphate causing hypocalcemia. Finally, the released purine nucleic acids are degraded into uric acid by xanthine oxidase leading to hyperuricemia. Acute renal failure is a potential consequence of acute tumor lysis syndrome that can further exacerbate these metabolic derangements. The primary event in the acute kidney injury is the crystallization of either uric acid or calcium phosphate in the renal tubules leading to obstructive nephropathy. However, hypovolemia, direct tumor cell infiltration, and drug-induced nephrotoxicity may also contribute to the development of acute kidney injury.

Tumor lysis syndrome typically occurs within 12–72 hours after initiation of anticancer therapy. Tumor lysis can even occur after low-dose anticancer medications or nontraditional anticancer therapies (e.g., steroids, interferon alpha, intrathecal methotrexate, rituximab, and radiation). There are also case reports of spontaneous development of tumor lysis syndrome as the presenting symptom of occult lymphomas. Children with preexisting renal injury as well as elevated uric acid and lactate dehydrogenase levels before anticancer therapy are at highest risk of tumor lysis syndrome.

Prevention and treatment of tumor lysis syndrome requires vigilant monitoring with attention to intravascular volume status, adequacy of urine output, and severity of metabolic abnormalities. All patients at risk for tumor lysis syndrome should receive liberal intravenous fluid therapy (usually 1 ½ times maintenance) to maintain adequate urine output (at least 1 mL/kg/hour with specific gravity of ≤1.010). The overall composition of the fluid may vary, but should *not* contain potassium or phosphorus.

Table 39.2 Cairo–Bishop classification for tumor lysis syndrome

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
LTLS	Absent	Present	Present	Present	Present	Present
Creatinine	<1.5 X Upper normal value	1.5 X Upper normal value	>1.5 to 3 X Upper normal value	> 3 to 6 X Upper normal value	> 6 X upper normal value	Death
Cardiac arrhythmia	None	Present, but requires no intervention	Present, requires nonurgent intervention	Present, symptomatic and partially controlled by medical therapy	Life-threatening; associated with heart failure, shock	Death
Seizure	None	None	Brief, isolated, generalized or few focal seizures controlled by medications; normal mental status	Poorly controlled recurrent seizures; altered consciousness	Status epilepticus	Death

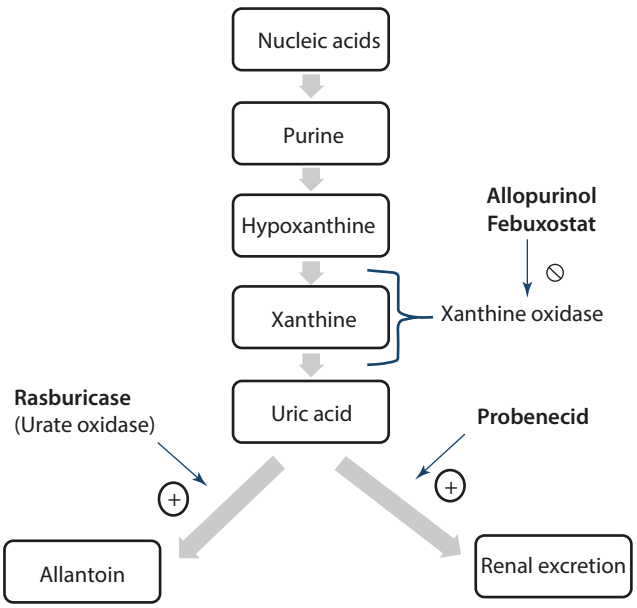
Reference: Cairo and Bishop (2004)

Cairo–Bishop defines laboratory tumor lysis syndrome (LTLS) when two or more of the following laboratory abnormalities are met within 3 days before or 7 days after initiation of chemotherapy: (1) serum calcium concentration decreases by 25% from baseline; (2) serum potassium concentration increases by 25% from baseline; (3) serum phosphorus concentration increases by 25% from baseline; (4) uric acid concentration increases by 25% from baseline

39.2.1.1 Hyperuricemia

In order to avoid renal injury, and to minimize the metabolic derangements of tumor lysis, it is crucial to aggressively prevent and treat hyperuricemia. This can be achieved either by: (1) preventing the formation of uric acid or (2) augmenting its elimination. In attempting to decrease production, it is essential to recognize that the purine nucleic acids are initially converted to hypoxanthine and then to uric acid via the enzyme xanthine oxidase (◘ Fig. 39.1). Allopurinol, a structural analog of hypoxanthine, is a competitive inhibitor of the enzyme xanthine oxidase. By competitively inhibiting xanthine oxidase, allopurinol decreases production of uric acid and results in a decrease in systemic uric acid levels. However, allopurinol has three key limitations. First, it only prevents the formation of new uric acid and does not enhance the elimination of uric acid formed prior to its administration. Second, it increases the levels of both xanthine and hypoxanthine, increasing the potential for xanthine crystallization and obstructive uropathy since xanthine is even less soluble in urine than uric acid. Third, allopurinol reduces the degradation of other purines requiring dose reductions in patients receiving medications such as 6-mercaptopurine.

In attempting to increase elimination, alkalinization of the urine can be utilized to augment the elimination of uric acid. Uric acid is insoluble at urine pH < 6.0 and will crystallize in the renal tubules, collecting ducts, and renal parenchyma. Systemic alkalinization can be used to produce alkaline urine (pH between 7.0 and 7.5) that increases the solubility of uric acid thereby facilitating renal elimination. Unfortunately, urine alkalinization decreases the solubility of calcium phosphate, and thus, may worsen renal function due to precipitation of calcium phosphate crystals in renal tubules. Moreover, the metabolic alkalosis may contribute to lower ionized calcium levels and/or fos-



◘ **Fig. 39.1** The pathway of uric acid production from nucleic acids and the sites of action of drugs used to treat hyperuricemia. As depicted in the diagram, allopurinol and febuxostat are inhibitors of xanthine oxidase and impede the production of uric acid. Rasburicase is a recombinant form of urate oxidase that catalyzes the conversion of uric acid to allantoin. Allantoin is significantly more soluble in urine than uric acid, and readily excreted by kidneys. Probenecid facilitates inhibition of the renal organic anion transporter protein, thereby blocking the reuptake of uric acid and fostering its excretion in the urine

In order to avoid renal injury, and to minimize the metabolic derangements of tumor lysis, it is crucial to aggressively prevent and treat hyperuricemia. Rasburicase, which catalyzes the conversion of uric acid to allantoin, has become the treatment of choice to prevent tumor lysis syndrome in children.

ter the formation of calcium and phosphate precipitants. Therefore, alkalinization is not preferred anymore in countries in which rasburicase (Elitex™ or Fasturtec™) is available to remove uric acid.

Rasburicase is a recombinant form of urate oxidase that catalyzes the conversion of uric acid to allantoin. Allantoin is significantly more soluble in urine than uric acid and readily excreted by the kidneys. Rasburicase has become the treatment of choice to prevent tumor lysis syndrome in children because it effectively reduces uric acid levels within 4 hours of administration and is more effective than allopurinol. Rasburicase is well tolerated with allergic reactions occurring in less than 1% of patients, but it should not be used in patients with glucose-6-phosphate dehydrogenase deficiency as it may induce severe hemolysis. Rasburicase may result in inaccurate serum uric acid levels as it may continue to breakdown uric acid in the laboratory collection tubes; this can be minimized by promptly placing the collection tube on ice.

39.2.1.2 Hyperphosphatemia

Hyperphosphatemia is often times difficult to treat. In addition to the release of intracellular phosphorus in conjunction with decreased renal function, hyperphosphatemia is exacerbated by up to four times more intracellular phosphorus in malignant cells than normal lymphoid cells. Moreover, anticancer therapy prevents the rapid uptake of phosphate by newly synthesized tumor cells. Calcium phosphate precipitants form when the calcium phosphorus solubility product (determined by multiplying the phosphorus concentration by the total calcium concentration) exceeds 60. Treatment must start by eliminating exogenous sources of phosphorus including any unnecessary medications with a phosphorus base. Phosphorus binding medications such as aluminum hydroxide (Amphojel®) and sevelamer (Renagel®) can be administered to decrease the gastrointestinal absorption. Sevelamer offers the advantage of not containing aluminum that may accumulate in the setting of renal failure. Intravenous glucose and insulin may also assist by driving phosphorus into the intracellular space, but this is a temporary measure. In the setting severe hyperphosphatemia, early institution of continuous veno-venous hemofiltration dialysis should be considered.

39.2.1.3 Hyperkalemia

Potassium levels >6.5 mEq/L or rapid increases in potassium (>2 mEq/L in 4 hours) can be associated with life-threatening dysrhythmias. Emergent measures to acutely decrease the serum potassium level must be implemented as described in the electrolyte section of this book (► Chap. 30). Sodium bicarbonate may be used to acutely decrease serum potassium levels by increasing the pH and driving potassium intracellularly. The administration of sodium bicarbonate may worsen ionized hypocalcemia, and one should be prepared to administer calcium in addition to bicarbonate when treating symptomatic hyperkalemia. Glucose and insulin may also be used to drive potassium intracellularly. Beta-agonist aerosol therapies may have the same effect. Sodium polystyrene sulfonate resins may be used to exchange sodium for potassium in the gastrointestinal tract. Loop diuretics (e.g., furosemide) facilitate urinary excretion of potassium. Continuous renal replacement therapy may be needed in extreme or refractory cases. Exogenous sources of potassium must obviously be eliminated as well as any medications that may result in elevated potassium levels (e.g., heparin, potassium-sparing diuretics, and angiotensin-converting enzyme inhibitors).

39.2.1.4 Hypocalcemia

Hypocalcemia resulting from hyperphosphatemia must be treated cautiously in order to prevent the formation of calcium phosphorus precipitants. Asymptomatic hypocalcemia should be monitored carefully and symptomatic manifestations of hypocalcemia such as seizures, tetany, and dysrhythmias should be treated. Intravenous infusion of either calcium gluconate or calcium chloride can be used.

39.2.1.5 Monitoring

In addition to the specific measures to prevent and treat the electrolyte disturbances of tumor lysis, vigilant clinical and laboratory monitoring is essential. Frequent clinical exams with focused attention on neuromuscular symptoms including, but not limited to muscle cramps, tetany, Chvostek and Trousseau signs, carpopedal spasms, paresthesias, twitching, weakness, lethargy, confusion, and seizures are necessary. Continuous electrocardiographic monitoring should be utilized to detect rhythm disturbances associated with the electrolyte imbalances. Although a variety of electrocardiographic changes may occur, hyperkalemia is most often associated with peaked T-waves and a widened QRS complex. Frequent assessment of fluid balance with particular attention to urine output is critical. Daily weights are used at some centers. Laboratory determinations that should be performed at least two or three times daily, and more frequently if the clinical status warrants, include complete blood cell counts as well as levels of uric acid, potassium, phosphorus, calcium, blood urea nitrogen, creatinine, lactate dehydrogenase, and urinary pH. Ionized calcium levels should also be measured as concomitant hypoalbuminemia may result in normal functional calcium levels.

39.2.2 Hyperleukocytosis Syndrome

Hyperleukocytosis is defined as a peripheral blood total white cell count more than 100,000 cells/μL (◘ Table 39.3). Hyperleukocytosis occurs more frequently in myeloid (5–22% in acute myeloid leukemia (AML) and 70–80% in chronic myeloid leukemia (CML)) versus lymphoid leukemia (9–13% acute lymphoblastic leukemia (ALL)). Factors associated with the development of hyperleukocytosis include age less than 1 year, male gender, massive hepatosplenomegaly, large mediastinal mass, T-cell phenotype in ALL, French-American-British (FAB) classification monocytic type M4/5 in AML, Philadelphia translocation (BCL-ABL1), chromosomal mixed-lineage leukemia (MLL) rearrangement 11q23, and FLT3-ITD mutation. Hyperleukocytosis is considered a poor prognostic factor and its presence often classifies the patient in a high-risk category.

Hyperleukocytosis augments the circulating blood viscosity due to an increase in the total leukocyte volume. The increased viscosity leads to sluggish microcirculatory flow and formation of leukocyte aggregates, which leads to leukostasis. Interestingly, there is no clear correlation between leukostasis and total leukocyte counts. Other cellular properties including myeloid cell type; expression of surface receptors CD11c and CD56; the release of TNF-α and IL1β; and the degree of up-regulation in expression of ICAM, VCAM, and E-selectin have all been associated with leukostasis. Additionally, rapid breakdown of leukocytes causes the release of tissue factor, which triggers activation of clotting via the extrinsic factor VII pathway. Finally, children with hyperleukocytosis develop varying intensity of tumor lysis syndrome. Most children with mild hyperleukocytosis are generally asymptomatic. However, total white

Table 39.3 Hyperleukocytosis syndrome clinical features and management

Variable	Factors
Definition Peripheral blood WBC > 100,000 cells/μL	Frequency of hyperleukocytosis syndrome associated with hematological malignancies: Chronic myeloid leukemia: 70–80% Acute myeloid leukemia: 11–22% Acute lymphoid leukemia: 9–13%
Risk factors	Age <1 year Male gender Large mediastinal mass T-cell phenotype acute lymphoid leukemia Philadelphia translocation Mixed-lineage leukemia (MLL) rearrangement
Clinical manifestations	Headache Blurry vision Cortical infarcts Dural sinus thrombosis Tumor lysis syndrome Disseminated intravascular coagulation (DIC)
Management	Cytoreduction treatment Leukopheresis only in symptomatic patients Treatment of tumor lysis syndrome Treatment of DIC

blood cell counts >200,000 cells/μL in myeloid leukemia or > 300,000 cells/μL in lymphoid leukemia often result in the clinical manifestations of hyperleukocytosis syndrome. The clinical presentation can be varied including headache, dyspnea, chest pain, pneumonitis, blurry vision due to retinal artery/vein occlusion, seizures, cortical infarctions, dural sinus thrombosis, tumor lysis syndrome, and in extreme cases, disseminated intravascular coagulopathy (DIC), hemorrhage, and multiorgan failure.

Total white blood cell counts > 200,000 cells/μL in myeloid leukemia or > 300,000 cells/μL in lymphoid leukemia often result in the clinical manifestations of hyperleukocytosis syndrome.

Management requires emergent initiation of cytoreduction treatment along with management of DIC and tumor lysis syndrome. The type of cytoreduction treatment is not standardized and the current practice varies from hydroxyurea only, low-dose cytoreduction, and standard-dose cytoreduction treatment. Leukopheresis is often used in symptomatic patients. However, prophylactic leukopheresis is not recommended due to the lack of outcome benefits over cytoreduction treatment and supportive care. Leukopheresis uses centrifugal force to separate leukocytes with about 15–70% reduction in total leukocyte count after one treatment. However, leukopheresis requires placement of a dialysis catheter and is associated with an increased risk of thrombocytopenia and hypocalcemia. Additionally, the overall response is short lived as the majority of cells are in the bone marrow. Moreover, there has been no demonstrated long-term clinical outcome benefit with this intervention.

39.2.3 Mediastinal Mass

The mediastinum is defined as the area of the thorax that extends from the superior aperture of the thorax to the diaphragm inferiorly and from the sternum and costal cartilages in front to the anterior surface of the 12 thoracic vertebrae behind. It is divided into three anatomic compartments; the anteriosuperior, the middle, and the posterior. Although relatively uncommon in

children, masses may arise in the mediastinum from a variety of both benign and malignant disorders. A review of several large series reveals non-Hodgkin lymphoma, Hodgkin lymphoma, and neuroblastoma to be the most common malignant diagnoses of mediastinal masses in children. Neural tumors arise from the posterior mediastinum and rarely produce any significant airway obstruction. Lymphomas typically arise from the anteriosuperior or middle mediastinum and can be associated with significant cardiopulmonary compromise.

39.2.3.1 Pathophysiology

The mediastinum is a closed space with minimal room for expansion. Masses that arise in that area act as space occupying lesions. As they expand, the structures in the mediastinum must be displaced and/or compressed. In the anteriosuperior and middle mediastinum, these compressed structures include the tracheobronchial tree, the heart, and the great vessels including the superior vena cava. Compression of any of these structures results in a condition known as the superior mediastinal syndrome. This syndrome has been associated with life-threatening airway obstruction, vascular compression resulting in impaired venous return to the heart, neurologic deficits, and death. The clinical presentation varies based on the site and severity of the anatomic obstruction or compression. For example, compression of the tracheobronchial tree may result in dyspnea, stridor, cough, orthopnea, and/or other respiratory symptoms. About 60% of children with mediastinal masses present with respiratory symptoms. Compression of the superior vena cava may cause venous engorgement, head and neck edema, and /or altered mental status. Direct cardiac compression may produce cyanosis, syncope, and dysrhythmias.

Superior mediastinal syndrome causes life-threatening airway obstruction, vascular compression resulting in impaired venous return to the heart and neurologic deficits.

Identifying patients at risk from these life-threatening complications is crucial. It is estimated that 7–19% of patients with a mediastinal mass may develop an airway complication with the induction of anesthesia or deep sedation. The pathophysiology of this airway compromise with anesthesia is multifactorial. With the induction of anesthesia, lung volumes are decreased secondary to weakened or abolished inspiratory muscle tone and increased abdominal muscle tone. Additionally, bronchial smooth muscle is relaxed resulting in increased compressibility of the large airways and decreased expiratory flow rates. This exacerbates the effects of the extrinsic compression. Third, the use of neuromuscular blockade eliminates the caudad movement of the diaphragm observed during spontaneous respiration, thereby, decreasing the transpleural pressure gradient. The transpleural gradient dilates the airways during inspiration, and when decreased, results in decreased airway caliber also augmenting the effect of the extrinsic compression. Additionally, supine positioning may result in further cephalad displacement of the diaphragm and increased central blood volume. This increased central blood volume results in increased blood being delivered to the tumor, increased tumor volume potentially worsening the obstruction.

39.2.3.2 Identification of High-Risk Patients

Any symptom of respiratory distress should raise concern of potential airway compromise with sedation. Orthopnea is particularly important in distinguishing patients at increased risk of compromise with anesthesia. The standard chest radiograph is also an important tool in the evaluation of a child with a mediastinal mass. Most importantly, it establishes the presence of a mediastinal mass as often these children are considered to have asthma or a similar process prior to the initial chest radiograph. In addition, the radiograph may also reveal

Although any symptom of respiratory distress should raise concern of potential airway compromise with sedation, *orthopnea* is particularly important in distinguishing patients with mediastinal masses at increased risk of compromise with anesthesia.

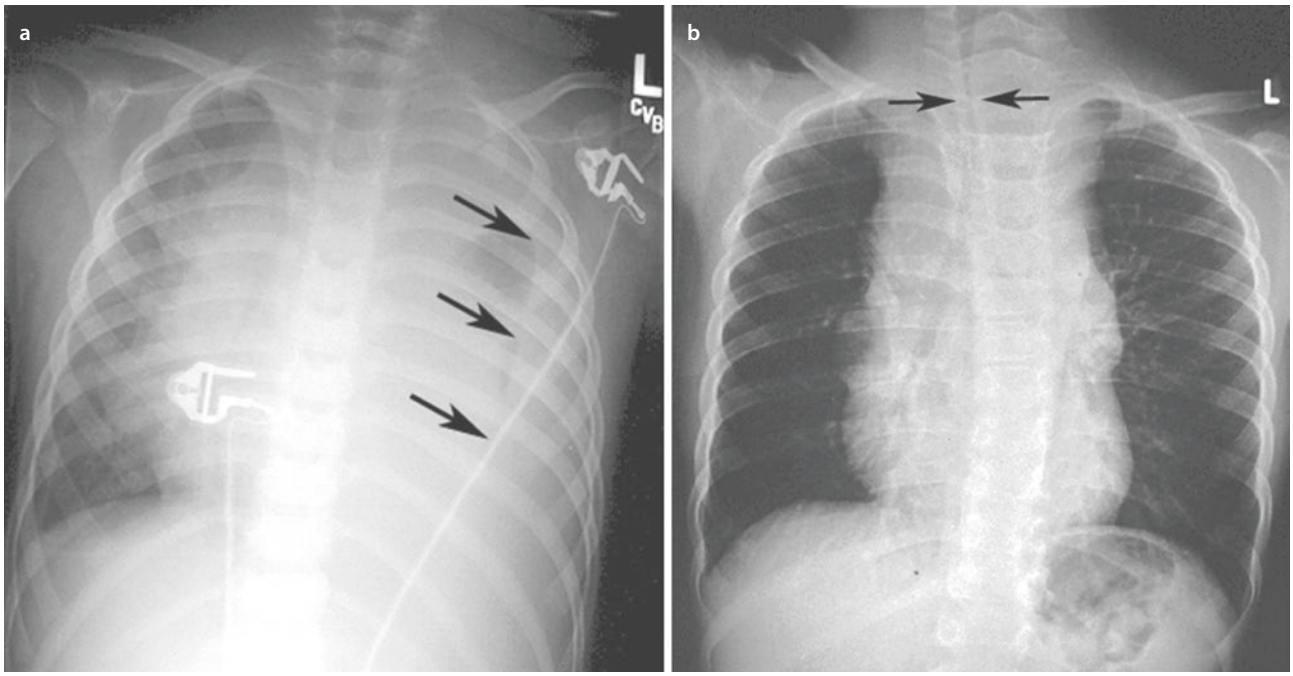


Fig. 39.2 Chest radiographs demonstrating pleural effusion (**a**, *arrows* demonstrate the edge of a large pleural effusion) and tracheal compression (**b**, *arrows* demonstrate narrowing of the trachea secondary to a mediastinal mass) associated with a mediastinal mass

Mediastinal masses that exceed 45% of the thoracic diameter on chest x-ray are more likely to be symptomatic than those that are less than 30% of the diameter.

Data suggest that general anesthesia may be safely administered if the tracheal cross sectional diameter is greater than 50% of the expected size on CT scan.

associated pleural effusions, tracheal compression, and/or tracheal deviation (Fig. 39.2). Masses that exceed 45% of the thoracic diameter on chest x-ray are more likely to be symptomatic than those that are less than 30% of the diameter. It should be noted, however, that patients at risk for airway compromise may have no tracheal compression observed on chest x-ray. Therefore, the chest radiograph is not very helpful for the management or determination of the risk for life-threatening airway compromise. Computed tomography (CT) of the chest may be more useful, accurately depicting mediastinal involvement, anatomical distortions, and the degree of tracheal compression. Additionally, data suggest that general anesthesia may be safely administered if the tracheal cross sectional diameter is greater than 50% of the expected size on CT scan.

Imaging studies are static tests of a dynamic process, and thus, dynamic studies may provide additional data. Pulmonary function tests have been used to identify patients at risk. Decreases in the peak expiratory flow rate (PEFR), total lung capacity, forced vital capacity, and forced expiratory volume in 1 second have all been reported in patients with a mediastinal mass suggesting both obstructive and restrictive deficits. The PEFR appears to be a useful predicator of airway compromise with a predicted PEFR <50% identifying patients at high risk for airway obstruction with the use of anesthesia. Also, a 12% decrease in pulmonary function can be anticipated when placing the child with a mediastinal mass in the supine, rather than, upright position. It is important to remember that these pulmonary function tests require patient cooperation in both the upright and supine positions often making their use impractical particularly in children. Figure 39.3 demonstrates the flow volume loops of a child with a mediastinal mass before and after therapy. Echocardiography is another dynamic test that may be used to assess cardiac function, the presence of a pericardial effusion, impending tamponade, and the integrity of the pulmonary outflow tract.

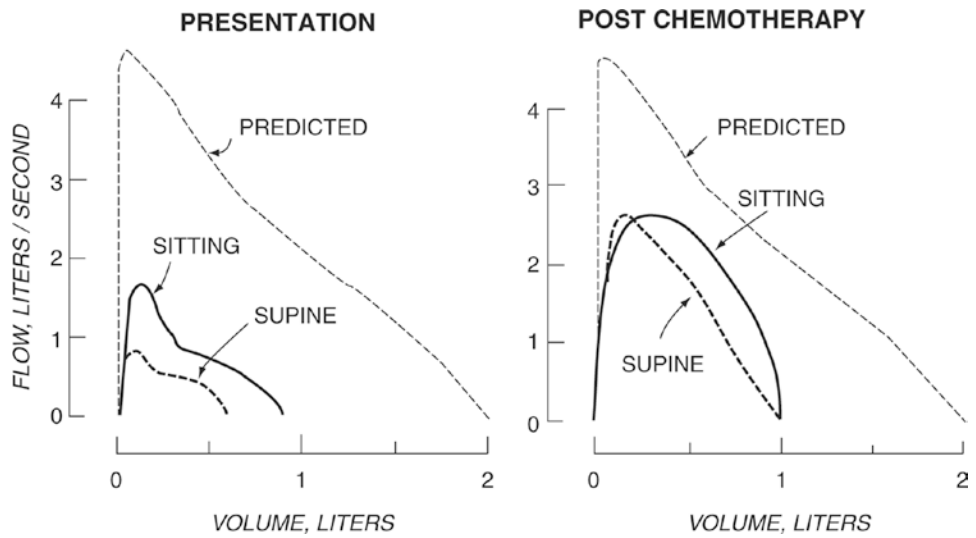


Fig. 39.3 Expiratory flow-volume loops of an 8-year old girl who presented with a large mediastinal lymphoblastic lymphoma. There was significant reduction in maximum flows, but this was markedly improved 4 days after the onset of chemotherapy (*right*). Note that the impairment was greater in the supine rather than the upright position. (Reprinted with Permission from Elsevier. Adapted from Shamberger et al. 1995)

39.2.3.3 Management and Approach to the Diagnostic Work-Up

Utilizing the data obtained from these clinical, radiological, and functional assessments, definitive work-up and treatment of the mass can proceed in a manner balancing the risk and the benefit. It is prudent to discuss the condition with all responsible clinical services (nursing, oncology, anesthesia, surgery, pathology, radiation oncology, and critical care) to assure the optimal course of action and the appropriate, timely handling of diagnostic specimens. A patient presenting with, or acutely developing, airway obstruction from a mediastinal mass is in a precarious condition of the highest magnitude. Several techniques may be used to decrease the obstruction and/or improve the airflow emergently. Repositioning the child from supine into upright, lateral, or prone position may be of benefit. Heliox may also improve air movement through the narrowed airway. Bag valve mask ventilation in a spontaneously breathing patient using high positive end expiratory pressure (PEEP) has been reported to be useful. If intubation is required, it is preferable to have it performed in the controlled environment of the operating room as described below. If emergent intubation must be performed outside the operating room, it should be performed without the use of neuromuscular blockade by the most experienced person. Reinforced endotracheal tubes of sufficient length to extend beyond the area of tracheal compression should be utilized. If at all possible, both a flexible and rigid fiberoptic bronchoscope should be available and cardiopulmonary bypass should be on standby. Once successfully intubated, the use of PEEP, repositioning of the tube, and/or repositioning of the patient may be needed to facilitate optimal air movement.

Although never ideal, presumptive, prebiopsy therapy may be required in cases of severe airway compromise. Clearly, this obviates the risks of anesthesia and delays in treatment associated with a diagnostic work-up. However, it may reduce the ability to make a definitive diagnosis, result in unnecessary therapy, and lead to improper staging of the disease. Prebiopsy radiotherapy has also been found to obscure the diagnosis.

In pursuing a definitive diagnosis, obtaining tissue from areas that are remote from the mediastinum may be performed and offer less risk. Such procedures may be performed under local anesthesia or with light sedation, but

with extreme caution nonetheless. For example, bone marrow aspiration may be used to ascertain a diagnosis, particularly for non-Hodgkin lymphoma. Unfortunately, this test may have less utility in other patient populations. Thoracentesis is another diagnostic test that may also be useful in determining the etiology of a mediastinal mass when associated with a pleural effusion. Among malignant masses, pleural effusions are more common in lymphoblastic lymphoma than in Hodgkin disease and this diagnosis has been secured using cytological and flow cytometric analysis of the pleural fluid. Fine needle aspiration and core needle biopsies of superficial lymphadenopathy have also been used to diagnose lymphoblastic lymphoma precluding the need for more invasive procedures. Excisional biopsies of these lymph nodes are more invasive, but still may be performed with local anesthesia and potentially yield more definitive results. If these other diagnostic approaches are unsuccessful, then a mediastinal biopsy must be considered. This may be performed via a percutaneous fine needle aspiration, via a CT-guided core needle biopsy, via mediastinoscopy, or via an open surgical excision.

39.2.3.4 Use of Anesthesia or Deep Sedation

If general anesthesia is deemed necessary, it must be approached with great caution in these high-risk children. First, secure intravenous access must be established and consideration should be given to lower extremity placement as the superior vena cava may have poor inflow due to extrinsic compression. Next, preanesthesia sedation or narcotics should be avoided. Both a flexible and rigid fiberoptic bronchoscope should be available and cardiopulmonary bypass should be on standby. The rigid, ventilating bronchoscope is the instrument of choice for the unstable airway. However, it is important to note that if the mediastinal mass is compressing the airway near or beyond the carina, a rigid bronchoscope may still be ineffective as it may not be able to open airways past the occlusion. Induction of anesthesia should be performed in an upright position; however, if the patient cannot tolerate this, then a lateral or prone position should be considered as supine positioning may be associated with worsening of the obstruction. Anesthesia should only be deepened once it is demonstrated that the patient can be easily ventilated with a bag mask set-up. The patient should be intubated with a reinforced endotracheal tube that is passed beyond the obstructed region. In the event of an acute airway occlusion, several maneuvers may be implemented that may be life-saving. Anesthetic effects should be reversed promptly and the patient returned to spontaneous ventilation. Repositioning of the child, in particular utilizing a prone position, may alter the effect of the mass on the airway and facilitate air movement. The ventilating rigid bronchoscope may be advanced beyond the area of obstruction. An emergent thoracotomy with bulk resection of the tumor may be performed to relieve pressure on the airway. However, this should be performed only in extremis as the bleeding and tissue edema involved may actually worsen the effects upon the mediastinum. If necessary, the patient may be placed on cardiopulmonary bypass or extracorporeal membrane oxygenation.

Even after a successful biopsy of the mass or lymph node, the postoperative recovery phase represents a time of continued high risk. During the immediate, postanesthetic period, the patient may still have impaired respiratory muscle function, altered level of alertness, and increased airway obstruction secondary to edema postbiopsy or partial resection.

Even after a successful biopsy of the mass or lymph node, the postoperative recovery phase represents a time of continued high risk. During the immediate, postanesthetic period, the patient may still have impaired respiratory muscle function, altered level of alertness, and increased airway obstruction secondary to edema postbiopsy or partial resection. Extubation should be attempted only after effective, spontaneous breathing has been documented. The patient will continue to require close monitoring for several days following initiation of therapy assessing for transient worsening from the edema associated with tumor lysis and to ensure response to treatment.

39.2.4 Cardiac Emergencies

Acute cardiac events are uncommon with a reported incidence of 0.9% to 2.5% in children undergoing cancer therapy or early post-HCT. However, cardiac toxicity remains a leading cause of long-term morbidity and mortality in cancer survivors. These patients have 9- to 15-fold higher odds of experiencing a cardiovascular event, chronic heart failure, or a coronary event compared to their healthy siblings. Common cardiac emergencies include acute heart failure, pericardial effusions, cardiac dysrhythmias, and pulmonary hypertension. Risk factors for cardiac toxicity include younger age, female sex, chemotherapeutic agents (cumulative anthracycline exposure and cyclophosphamide and new immunotherapies), mantel or total body radiation, a persistent inflammatory state, transfusion-related iron overload, cumulative fluid overload, genetic predisposition, sickle cell disease, underlying cancer type, and HCT.

The pathophysiology of cardiac toxicity is complex and often multifactorial. Some well-described mechanisms include radiation-induced fibrosis, chronic inflammation, activation of the renin-angiotensin-aldosterone system (RAAS), and anthracycline-induced cardiac myocyte damage. Other potential mechanisms include microvascular endothelial injury, thromboembolic events, pituitary and adrenal dysfunction, exposure to oxygen reactive species, iron overload, mitochondrial dysfunction, and chronic arterial hypertension.

Potential mechanisms of cardiac toxicity in pediatric oncology patients include radiation-induced fibrosis, chronic inflammation, activation of the renin-angiotensin-aldosterone system (RAAS), anthracycline-induced cardiac myocyte damage, microvascular endothelial injury, thromboembolic events, pituitary and adrenal dysfunction, exposure to oxygen reactive species, iron overload, mitochondrial dysfunction and chronic arterial hypertension.

39.2.4.1 Monitoring and Diagnosis

There are limited evidence-based consensus guidelines regarding cardiovascular monitoring for children undergoing cancer therapy. Most centers do perform pretreatment electrocardiograms and echocardiograms (ECHO). Some centers measure serial biomarker profiles (i.e., troponin, brain natriuretic peptide, high sensitivity C reactive protein, and myeloperoxidase). A few centers use cardiac Magnetic Resonance Imaging (MRI) and Positron Emission Tomography with MRI. A detailed discussion on each of these individual modalities is beyond the scope of this chapter.

39.2.4.2 Management

Early recognition, timely intervention, and close monitoring of cardiac function is a must for the effective treatment of cardiac toxicity in children undergoing cancer treatment or HCT. Correction of electrolyte abnormalities and removing medications causing prolonged QTc are needed to abate cardiac dysrhythmias. Those with symptomatic pericardial effusions (tachycardia, narrow pulse pressure, pulsus paradoxus, and Kussmaul sign) or tamponade physiology (low cardiac output state, ECHO findings of right atrium and right ventricle collapse) need volume resuscitation to optimize preload and emergent ECHO-guided percutaneous pericardiocentesis with or without drain placement. Recurrent pericardial effusions often require a pericardial window or total pericardiectomy. Diuretics or inotropic medications are not indicated and may worsen hemodynamics in patients with a symptomatic pericardial effusion. The role of immunomodulators such as systemic steroids and antiinflammatory agents is not well defined in this population. Epstein Barr Virus (EBV) – positive pericardial effusions often respond to decreasing the intensity of immunosuppression and by the use of rituximab to target CD20 positive B-cells. Patients with thrombotic microangiopathy (TMA) – associated effusions have shown improvement after plasmapheresis and eculizumab (anti-C5 complement antibody). Eculizumab binds to the terminal component of complement 5 and inhibits the conversion of C5 to activated C5a. By halting the production of C5a, a potent anaphylatoxin, the proinflammatory and prothrombotic process is tempered. Acute heart

failure management often requires invasive hemodynamic monitoring, initiation and titration of vasoactive-inotropic medications (usually low dose epinephrine, milrinone and/or vasopressin) based on markers of cardiac output and estimation of systemic vascular resistance, diuretics for fluid overload, mechanical ventilation support to decrease oxygen demand and reduce left ventricular afterload, and eventually, transitioning to oral afterload reduction (angiotensin-converting enzyme inhibitors) and rate control (beta-blockers) medications in close collaboration with a heart failure specialist. Pulmonary hypertension is well described in children with sickle cell disease and is increasingly recognized in children with oncological diseases and HCT. Children with transplant associated-TMA have been found to have elevated right-sided cardiac pressure on day +7 of HCT compared to those who did not develop TMA (60% vs. 32%). The treatment of pulmonary arterial hypertension in children with sickle cell disease and other oncological diseases is similar to other populations.

39.2.5 Neurological Emergencies

Neurological complications are associated with significant morbidity and mortality in children with cancer. These complications may be due to direct involvement of the central nervous system (CNS) by cancer or indirectly due to anticancer therapies. Seizures are the most common manifestation and may be present in up to 50% of patients with neurologic complications. Other manifestations include acute encephalopathy, focal motor or sensory deficits, cranial nerve palsies, peripheral neuropathies, and impaired coordination. The differential diagnosis includes CNS infection, drug-induced neurotoxicity, drug-induced delirium, severe electrolyte abnormalities, paraneoplastic syndrome, and leptomeningeal or intracranial metastatic tumor spread. A child presenting with an acute neurological complication requires a prompt evaluation and often needs frequent ongoing neurological monitoring. The diagnostic work-up should be tailored to the particular patient by taking into consideration all of the following: the patient's age, the presenting neurological symptoms and signs, the type and location of the primary cancer, recent cancer therapies, and the severity of immunosuppression. Many of these patients need emergent neurological imaging, a lumbar puncture for cerebrospinal fluid analysis and continuous electroencephalogram monitoring for seizure management. It is prudent to involve the neurology and the primary oncology team early in the course to guide clinical management.

39.2.5.1 Posterior Reversible Encephalopathy Syndrome (PRES)

The common MRI findings of posterior reversible encephalopathy syndrome (PRES) are symmetric bilateral occipital and parietal lobe subcortical white matter involvement.

Posterior reversible encephalopathy syndrome (PRES) is an increasingly recognized neurological complication in children with cancer. It is also known as reversible posterior leukoencephalopathy syndrome (RPLS). The incidence of PRES has been reported to be 0.3–3% in children with cancer. Younger age, underlying hematological malignancy, induction phase of chemotherapy especially intrathecal dosing, post-HCT, high dose steroid, and cyclosporine and tacrolimus use are the commonly reported risk factors. Common clinical manifestations include seizures, hypertension, altered mental status, visual disturbances, and cortical blindness. MRI brain imaging with T2 weighted and FLAIR sequence is often performed to confirm the diagnosis. The common MRI findings are symmetric bilateral occipital and parietal lobe subcortical white matter involvement (◘ Fig. 39.4). The treatment of PRES includes seizure control and prophylaxis, hypertension control using oral and intravenous agents, correction of electrolyte abnormalities, and discontinuation of implicated medications, if possible.

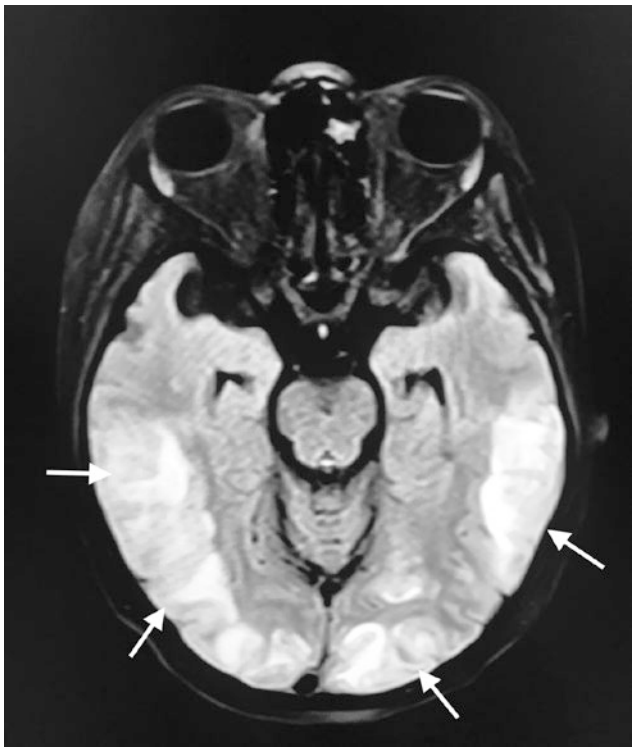


Fig. 39.4 MRI head demonstrating symmetric large confluent areas of abnormal parenchymal T2 FLAIR hyperintense signal (white arrows) prominently involving bilateral temporal lobes (lateral aspects), and bilateral occipital lobes (posteriorly) consistent with the posterior reversible encephalopathy syndrome (PRES)

39.2.5.2 Spinal Cord Compression

Compression of the spinal cord has been reported to occur in 2.5–5% of children with cancer. Epidural compression of the spinal cord by spread of a paravertebral tumor through an intervertebral foramina is the most frequent etiology. Epidural compression compromises vertebral venous plexus flow leading to local vasogenic ischemia, hemorrhage, and edema. The majority of spinal cord compressions occur due to metastatic tumor spread rather than primary spinal tumors. Some common tumors associated with spinal cord compression include Ewing sarcoma, neuroblastoma, neuroectodermal cell tumors, lymphomas, and germ cell tumors. The treatment of spinal cord compression requires emergent intravenous dexamethasone followed by either immediate decompressive laminectomy or targeted chemotherapy and radiation therapy based on the underlying tumor pathology.

The majority of spinal cord compressions occur due to metastatic tumor spread instead of primary spinal tumors.

The treatment of spinal cord compression requires emergent intravenous dexamethasone followed by either immediate decompressive laminectomy or targeted chemotherapy and radiation therapy based on the underlying tumor pathology.

39.2.6 Infections

Infections are a major cause of morbidity and mortality in children with cancer. Children with cancer often have impairment of host defenses including neutropenia, impaired cellular (T-cell, NK-cell) and humoral immunity (B-cell), reticuloendothelial system dysfunction, and disruption of skin and mucosal barriers due to anticancer therapies (Table 39.4). These impairments may be inherently related to certain immune cell cancers, but mostly are associated with cytotoxic and immunosuppressive anticancer therapies. Recently, the use of immunotherapies has substantially increased the risk of infections. Impaired host defenses put children with cancer at increased risk of

Table 39.4 Common typical and atypical infections in children with cancer

Infections	Risk factors	Treatment Considerations*
Hematological infections		
Gram-positive cocci Staphylococcus aureus Coagulase negative staphylococcus Streptococcus viridans Enterococci	Prolonged neutropenia Indwelling catheter Mucositis	Vancomycin +/– nafcillin Penicillin G for *Streptococcus viridans* Linezolid for vancomycin resistant enterococci
Gram-negative bacilli Escherichia Coli Klebsiella pneumonia Pseudomonas aeruginosa	Prolonged neutropenia Indwelling catheter Hospital acquired Exposure to antibiotics	Cefepime Meropenem or Imipenem
Salmonella infections S. Typhimurium S. Dublin	Contaminated food	Ceftriaxone followed by transition to oral azithromycin or a fluoroquinolone
Corynebactrium jeikeium	Prolonged neutropenia Prolonged hospital stay	Vancomycin
Bacillus species	Indwelling catheter Total parenteral nutrition	Vancomycin plus aminoglycosideCeftriaxone followed by transition to oral azithromycin or a fluoroquinolone
Mycobacterium fortuitum (Actinobacteria)	Hospital acquired Skin incisions	Initial therapy for serious disease is amikacin plus meropenem, followed by at least 4-month treatment with two antibiotics such as ciprofloxacin, amikacin and cefoxitin
Invasive fungal infections Candida species Aspergillus fumigatus and flavus Malassezia furfur Cryptococcus neoformans Fusarium species	Exposure to antibiotics Prolonged immunosuppressed state Indwelling catheters Total parenteral nutrition	Amphotericin B as initial starting therapy or when treating neonates with CNS disease. Voriconazole is the drug of choice for invasive aspergillosis
Adenovirus	Community acquired Impaired cellular immunity	Cidofovir
Respiratory infections		
Common respiratory viral infections Respiratory syncytial virus Influenza viruses Parainfluenza viruses Human metapneumovirus Rhinovirus Enteroviruses Adenovirus	Community acquired More severe disease	Supportive therapies Oseltamivir – Influenza Cidofovir – Adenovirus

Table 39.4 (continued)

Infections	Risk factors	Treatment Considerations*
Bacterial pneumonias Staphylococcus aureus Streptococcus pneumoniae Hemophilus influenzae Escherichia Coli Klebsiella pneumoniae Pseudomonas aeruginosa	Prolonged neutropenia Mechanical ventilation	Vancomycin +/– nafcillin Plus Cefepime if gram negative bacilli are suspected
Mycoplasma pneumoniae	Community acquired	Macrolides (azithromycin)
Invasive fungal infections Aspergillus fumigatus and flavus Mucorales Blastomyces Histoplasma capsulatum	Impaired cellular immunity Hematopoietic cell transplant Iron overload	Amphotericin B plus echinocandin as the initial starting therapy +/– surgical debridement; Voriconazole for Aspergillus
Pneumocystis jiroveci pneumonia	Impaired cellular immunity	Trimethoprim-sulfamethoxazole
Mycobacterium tuberculosis Primary Reactivation	Impaired cellular immunity Contact exposure	Isoniazid and rifampicin 6 months followed by maintenance therapy
Adenovirus	Impaired cellular immunity	Cidofovir
Central nervous system (CNS) infections		
Listeria monocytogenes	Impaired cellular immunity	Ampicillin +/– gentamicin
Toxoplasma gondii	Impaired cellular immunity	Pyrimethamine and sulfadiazine Folinic acid to minimize toxicity
Cryptococcus neoformans	Impaired cellular immunity	Amphotericin B plus azoles Induction with amphotericin B and flucytosine for at least 2 weeks followed by consolidation with amphotericin B and fluconazole for at least 8 weeks
Nocardia asteroides	Impaired cellular immunity	Trimethoprim-sulfamethoxazole Plus imipenem and amikacin for serious disease
CNS invasive fungal disease Candida species Aspergillus fumigatus and flavus Mucorales	Impaired cellular immunity Sinopulmonary disease Indwelling catheter Total parenteral nutrition	Amphotericin B as the initial starting therapy or when treating neonates Voriconazole for aspergillosis
Polyomavirus (JC virus)	Impaired cellular immunity	Supportive care

*These are simply general considerations and any treatment choices should be verified with a more appropriate resource and/or a Pediatric Infectious Disease. Specialist

life-threatening infections from conventional pathogens and various opportunistic pathogens. It is challenging to identify and differentiate an opportunistic infection early due to lack of reliable clinical signs/symptoms, and the poor host response limits diagnostic tools in these patients. Therefore, physicians must be aware of the potential risk of opportunistic infections associated with various immunosuppressive and immunotherapy. In the following section, some common opportunistic infections reported in children with cancer will be reviewed.

39.2.6.1 Hematological Infections

Gram-positive bacteria such as coagulase negative *Staphylococci* and *Streptococcus viridans* are the most common pathogens isolated in the neutropenic host with a bloodstream infection.

Bloodstream infections with conventional pathogens are common in neutropenic children with cancers. These infections remain frequent despite efforts to provide an aseptic environment and antimicrobial prophylaxis. Gram-positive bacteria such as coagulase negative *Staphylococci* and *Streptococcus viridans* are the most common pathogens isolated in the neutropenic host. However, many institutions are reporting trends toward more frequent Gram-negative bacilli such *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*. Other opportunistic bacteremia reported with varying incidence in this population includes Salmonella infections (*S. typhimurium, S. dublin, and S. enteritidis*), *Corynebacterium jeikeium*, Bacillus species, and *Mycobacterium fortuitum*.

39.2.6.2 Invasive Fungal Infections

Major risk factors for invasive fungal infections include neutropenia <500 cells/μL for >10 days, hematological malignancies, hematopoietic cell transplant, prolonged steroid treatment (>4 weeks), undergoing an invasive procedure, major surgery, prolonged total parental nutrition (>4 weeks), and ICU stay >3 weeks.

Invasive fungal infections (IFI) are a significant medical problem in immunocompromised children with cancer. The exact incidence of invasive fungal infections is undetermined, but it varies from 5% to 25% in patients with leukemia and HCT. Major risk factors for IFI include neutropenia <500 cells/μL for >10 days, hematological malignancies, HCT, prolonged steroid treatment (>4 weeks), undergoing an invasive procedure, major surgery, prolonged total parental nutrition (TPN)(>4 weeks), and ICU stay >3 weeks. Candida species (50% of cases) and Aspergillus species are the most common IFI isolated from immunocompromised patients. Other reported etiologies of IFI include Cryptococcus species, Fusarium species, Zygomycete species, and Dematiaceous fungi.

39.2.6.3 Hematogenous Fungal Infections

Acute hematogenous candidiasis (AHC) is a frequent presentation of invasive hematogenous fungal infections. *Candida albicans* is the most common cause of AHC, followed by *Candida tropicalis* and *Candida krusei*. *Candida parapsilosis* is associated with TPN use. Surveillance blood cultures have limited value in the detection of AHC as only 20–35% patients have a positive blood culture. A high level of clinical suspicion is needed in patients with known risk factors, who have persistent or relapsing fever despite antibiotics, maculopapular rash, myalgia, and new or persistent thrombocytopenia. Fungal endophthalmitis is a frequent complication of AHC which manifests as headache, blurry vision, and/or orbital pain. A surveillance eye examination is indicated in patients diagnosed with AHC. Conventional or liposomal Amphotericin B is the drug of choice for the treatment of AHC. Other alternatives include azoles (fluconazole or voriconazole) and micafungin. *Malassezia furfur* is a part of the cutaneous commensal flora and is associated with a wide spectrum of fungal infections. Debilitated patients supported with TPN are prone to fungemia with Malassezia due to its lipophilic properties. Treatment includes Amphotericin B, removal of the central venous catheter, and discontinuation of TPN.

39.2.6.4 Pulmonary Infections

Impaired local and systemic defense mechanisms put children with cancer or those undergoing HCT at high risk for serious upper and lower respiratory tract infections from either common or opportunistic microorganisms. Progression of these respiratory infections to lower respiratory tract increases morbidity and mortality in immunocompromised children especially those with HCT. These patients are at risk of serious respiratory infections due to common viral or bacterial pathogens occurring in healthy children such as bacterial pathogens (*Streptococcus pneumoniae, Staphylococcus aureus,* and *Hemophilus influenzae*), viral pathogens (respiratory syncytial virus, influenza viruses, parainfluenza viruses, human metapneumovirus, rhinovirus, enteroviruses, and adenovirus), and atypical bacteria (*Mycoplasma pneumoniae*). These patients are also at risk for hospital-acquired pathogens especially, methicillin resistant *Staphylococcus aureus*, enteric Gram-negative bacilli, and *Pseudomonas aeruginosa*. Also, they are at risk for opportunistic infections from atypical organisms such as invasive aspergillosis, mucormycosis, *Pneumocystis jiroveci pneumonia*, and cytomegalovirus pneumonitis and reactivation of dormant infections such as mycobacterium, *Histoplasma capsulatum*, Herpes simplex virus, and Herpes varicella-zoster. In the following section, we briefly discuss a few of the opportunistic pulmonary infections.

39.2.6.5 Invasive Sinopulmonary Fungal Disease

Invasive aspergillosis is commonly caused by *Aspergillus fumigatus* and *Aspergillus flavus*. Exposure to aspergillus conidia is frequent, but in an immunocompromised host with an ineffective immune response, aerosolized aspergillus conidia enter the body through the sinopulmonary tract. Once in the body, these conidia can germinate into fungal hyphae and invade pulmonary arteries leading to pulmonary artery thrombosis, pulmonary hemorrhage, and lung tissue necrosis. Clinical manifestations include persistent or relapsing fever, pleuritic chest pain, and persistent dry cough. Dyspnea, hypoxemia, and hemoptysis are late clinical features associated with advanced disease. The typical radiological findings include a nodule or nodules surrounded by a halo of ground-glass attenuation "halo sign" or late findings of the "air-crescent sign" due to the separation of necrotic lung tissue from the surrounding parenchymal tissue. However, it is important to recognize that these findings are not specific to aspergillosis and can be observed in other invasive fungal diseases, and in pediatric patients, radiological findings are more variable and mostly nonspecific. The diagnosis should be promptly established with bronchoalveolar lavage (BAL) or computerized tomography (CT) guided biopsy of lung lesions. Monotherapy with voriconazole is the initial recommended therapy. For severe and aggressive disease, a combination therapy with voriconazole and an echinocandin is recommended. Empiric therapy with Amphotericin B can be considered if the diagnosis of aspergillosis is not yet established or if the patient has recently been treated with azoles. Approximately 10–15% of patients can have CNS dissemination of the disease. Those with severe and disseminated invasive aspergillosis especially HCT-recipients have mortality rates as high as 80%.

Similar to invasive aspergillosis, mucormycosis is an angio-invasive fungal disease. Mucormycosis occurs less frequently, but is a far more aggressive disease than invasive aspergillosis. Mucormycosis often disseminates to the lungs, sinuses, orbital cavity and, in rare cases, the CNS. Risk factors include an immunosuppressed state, status post HCT, diabetes mellitus, iron overload, and exposure to deferoxamine. The clinical presentation and radiological findings are not very helpful in differentiating between mucormycosis and invasive

aspergillosis. Treatment of mucormycosis involves a combination of antifungal therapy and surgical debridement of infected tissue. Amphotericin B is the drug of choice for initial antifungal therapy and should be continued until there is clinical resolution of the disease. Posaconazole can be used as step-down therapy as most patients need antifungal therapy for weeks, and longer if an immunocompromised state persists. Overall, mortality from invasive mucormycosis with CNS involvement ranges from 25% to 65%.

39.2.6.6 Pneumocystis Jiroveci Pneumonia

PJP is treated with TMP-SMX. Pentamidine can be used with caution as an alternative agent for those allergic to sulfa-containing drugs.

Pneumocystis jiroveci pneumonia (PJP) is a frequent fungal infection in children with impaired cellular immunity. Clinical manifestations include dry cough, dyspnea, and progressive hypoxemia, often out of proportion to the radiographic lung findings. The characteristic radiographic findings are bilateral symmetric interstitial infiltrates; other findings may include consolidations, nodules, unilateral infiltrates, and/or pneumatoceles. CT-imaging often reveals ground glass opacities with thickening of the interlobular septa. Bronchoscopy with BAL is a safe and sensitive test to confirm the PJP diagnosis. PJP is treated with trimethoprim-sulfamethoxazole (TMP-SMX). Pentamidine can be used with caution as an alternative agent for those allergic to sulfa-containing drugs. Pentamidine can cause serious adverse effects such as bronchospasm, cardiac arrhythmias, hypotension, hypoglycemia, and azotemia. Prophylactic treatment with trimethoprim-sulfamethoxazole (TMP-SMX) or pentamidine is recommended in patients undergoing HCT for up to 6 months and those with severely impaired cellular immunity.

39.2.6.7 CNS Infections

As a result of their immunocompromised state, children with cancer are at risk of developing various opportunistic CNS infections. Common clinical manifestations of CNS infection include seizures, encephalopathy, persistent headaches, visual deficits, and new neurological sensory or motor deficits. A prompt infectious work up including cerebrospinal fluid microbiological analysis and appropriate CNS imaging is needed to delineate the etiology. *Listeria monocytogenes*, *Toxoplasma gondii*, *Cryptococcus neoformans*, *Nocardia asteroides*, and polyomavirus can occur in those with impaired cellular immunity. CNS disease, as a local or hematogenous spread of invasive fungal disease (e.g., candidiasis, aspergillosis, and mucormycosis), can occur in those with prolonged neutropenia.

39.2.7 Febrile Neutropenia

Febrile neutropenic patients can be classified into a high-risk category based on the duration of neutropenia (>7 days), the degree of neutropenia (≤100 cells/μL), associated multiorgan dysfunction (renal or liver insufficiency), and hemodynamic instability.

Febrile neutropenia is defined as fever (temperature > 100.3 °F) and an absolute neutrophil count (ANC) ≤500 cells/μL. Febrile neutropenia is a serious life-threatening complication of chemotherapy, which requires prompt recognition and initiation of appropriate antimicrobial therapy. These patients often have no or minimal symptoms of bacterial/fungal infection. The initial examination requires close examination of common sites of infection such as the skin, oropharyngeal mucosa, respiratory tract, gastrointestinal tract, and genitourinary tract. Also, any site with a recent or active indwelling catheter requires thorough examination. Additionally, blood cultures should be obtained from all lumens of an indwelling central venous catheter as well as from a peripheral blood site. A chest radiograph should be performed in those with respiratory symptoms. These patients can be classified into a high-risk category based on the duration of neutropenia (>7 days), the degree of neutropenia (≤100 cells/μL), associated multiorgan dysfunction (renal or liver insufficiency), and hemodynamic instability. It is recommended to adopt a validated risk stratification strategy and to incorporate this strategy into clinical practice.

Based on the most current guidelines, pediatric patients with febrile neutropenia who are clinically stable and have no risk factor can be empirically treated intravenously by monotherapy with an antipseudomonal beta-lactam penicillin (i.e., piperacillin–tazobactam or ticarcillin–clavulanic acid), an antipseudomonal cephalosporin (i.e., cefepime or ceftazidime), or a carbopenem (i.e., meropenem and imipenem). However, the addition of a glycopeptide (i.e., vancomycin) and a second gram-negative agent should be strongly considered for patients who are clinically unstable, who have associated high-risk factors, or when a resistant infection is suspected. The most appropriate antibiotic coverage for high-risk patients is a combination of two antipseudomonal agents such as a beta-lactam penicillin (i.e., piperacillin–tazobactam or ticarcillin-clavulanic acid), an antipseudomonal cephalosporin (i.e., cefepime or ceftazidime), or a carbapenem (i.e., meropenem or imipenem), and the addition of a glycopeptide (i.e., vancomycin).

Empiric antifungal therapy is not recommended for routine use in low-risk patients. Antifungal therapy should be considered in patients who are at high risk for invasive fungal infection including patients with acute myeloid leukemia, relapsed acute lymphoid leukemia, on highly myelosuppressive chemotherapy for other malignancies and allogeneic HCT recipients with persistent fever despite prolonged (≥4 days) broad spectrum antibiotic therapy and expected duration of neutropenia (≥10 days).

Antimicrobial treatment should be continued until the patient is afebrile for more than 48 hours and clinically stable, has at least two consecutive negative blood cultures, and has recovery of neutrophil count >500 cells/μL. For the patient with a causative agent identified, the treatment duration depends on the organism and the site of infection. Early consultation with an infectious disease specialist with expertise in oncological diseases is often required because most of these patients have extensive prior history of infections and exposure to various antimicrobial agents. Antimicrobial prophylaxis with fluoroquinolone (i.e., ciprofloxacin and levofloxacin) is recommended for high-risk patients with prolonged neutropenia (>7 days). Also, patients who have undergone HCT or who received salvage/intensive chemotherapy for acute leukemia are considered high risk for an invasive fungal disease during the prolonged period of severe neutropenia. Antifungal prophylaxis with either an azole (i.e., fluconazole, itraconazole, and posaconazole) or an echinocandin (i.e., micafungin and capsofungin) class agent is highly recommended in these patients. Granulocyte-colony stimulating factor, (G-CSF) such as filgrastim or pegfilgrastim, is often used to prevent chemotherapy-induced neutropenia in high-risk patients with solid or nonmyeloid cancers. G-CSF can also be used in patients with solid or nonmyeloid cancers to reduce time for recovery of neutrophil count during a febrile neutropenia episode.

39.2.8 Special Considerations in Sepsis

Children with cancer often undergo aggressive treatment with chemotherapy, radiation, and surgery. These intensive therapies usually require placement of indwelling catheters, frequent procedures and/or catheter access, and commonly lead to a prolonged immunosuppressed state, which substantially increase the risk of typical and atypical opportunistic infections in these patients. Children with cancer, particularly those with high-risk hematological malignancies and post-HCT, are prone to develop severe sepsis and shock and have higher sepsis-related mortality (17–25% in those with cancer without HCT and 30–45% in those post-HCT) compared to children without cancers (8–15%). Also, mortality can exceed 70% if three or more organs are dysfunctional.

The risk, severity and type of infection in children with cancer varies based on the site of infection, the type of underlying cancer, the regimen of anticancer therapy, the phase of anticancer therapy (e.g., induction, delayed intensification, or maintenance), and relapsed or recurrent disease status, as well as the duration and severity of the immunosuppressed state.

Although the majority of the management of severe sepsis and septic shock is similar to that in other children and should be based on the recommendations of the published consensus guidelines, there are some important considerations when treating a cancer patient with severe sepsis or septic shock. First, it is important to characterize the risk of infection and the baseline multiorgan functional status to individualize treatment plans. Risk, severity, and type of infection often vary based on the initial site of infection, the type of underlying cancer, the regimen of anticancer therapy, the phase of anticancer therapy (e.g., induction, delayed intensification, or maintenance), the relapsed or recurrent disease status, and the duration and severity of the immunosuppressed state. In patients who have received or are undergoing HCT, the risk depends on the type of conditioning regimen, the type of HCT, first versus previously failed HCT, and the phase of HCT (e.g., preengraftment and postengraftment or >100 days post-HCT). Other essential information includes history of documented infections, past antimicrobial therapies and antimicrobial prophylaxis, and recent steroid use and anticancer therapy-induced organ dysfunction (e.g., radiation/bleomycin-induced acute lung injury, doxorubicin-related dilated cardiomyopathy, steroid/radiation-related restrictive cardiomyopathy, cisplatin-induced acute tubular kidney injury, peg-asparaginase-induced acute pancreatitis, and decarbazine-induced acute liver injury).

The initial diagnostic evaluation includes a complete blood cell count, basic chemistry values, aerobic and anaerobic blood cultures, urine culture, and chest radiograph. Adequate blood volume should be obtained from each lumen of the central indwelling catheter for culture. The Infectious Disease Society of America recommends weight-based criteria (blood volume preferably >2 mL), and if <10 mL of blood is obtained, blood should be placed in a single aerobic bottle rather than divided between aerobic and anaerobic bottles. As patients with an immunosuppressed state are more prone to atypical pathogens, they often require more specialized studies such as tissue biopsy or BAL; stool samples for common enteric pathogenic bacterial panel, *Clostridium difficile* toxin, ova/parasites, and viral particles; fungal cultures; respiratory viral polymerase chain reaction (PCR) panel; and blood viral PCR studies. The specifics of the diagnostic work up should preferably be guided by infectious disease specialists. In selective cases with high risk for invasive fungal disease, CT-imaging of the sinuses, chest, abdomen, and pelvis must be considered to determine the extent of fungal disease. At times, it is required to obtain serial levels of markers of inflammation including C-reactive protein (CRP), procalcitonin (PCT), serum ferritin, and cytokines (e.g., IL-6, IL-8, and IL-10) to differentiate between bacterial and viral pathogens, to identify patients with cytokine release syndrome and secondary HLH, or to monitor the response to therapy. Data on the utility of such biomarkers and the impact on overall outcome among these patients are limited. Finally, serial measurement of markers of oxygen delivery (e.g., serum lactate concentration and mixed venous oxygen saturation); markers of organ function such as brain natriuretic peptide (BNP), creatinine, cystatin C, serum liver enzyme levels, lactate dehydrogenase concentration, coagulation profile, and advanced hemodynamic monitoring (central venous pressure, echocardiography, pulse contour cardiac output monitor (PiCCO), and lithium dilution cardiac output monitor (LiDCO)) may be useful to guide resuscitation, blood product transfusion, and vasoactive inotropic support in these patients.

Empiric antimicrobial therapy should be given intravenously and preferably within 1 hour of presentation. The most appropriate antibiotic coverage should be a combination of two antipseudomonal agents such as a beta-lactam penicillin (i.e., piperacillin-tazobactam or ticarcillin-clavulanic acid), an antipseudomonal cephalosporin (i.e., cefepime or ceftazidime) or a carbapenem (i.e., meropenem or imipenem), an aminoglycoside (i.e., gentamicin), and a glycopeptide (i.e., vancomycin). Empiric antifungal therapies with azoles or echinocandins should be considered in those with high risk of invasive fungal disease or persistent fever despite prolonged (≥4 days) antibiotic therapy and anticipated duration of neutropenia (≥10 days) in consultation with an infectious disease specialist. Early removal of an infected indwelling central venous catheter should be strongly considered in the presence of specific pathogens such as *Pseudomonas aeruginosa*, Bacillus species, vancomycin-resistant Enterococci species, *Stenotrophomonas maltophilia*, *Corynebacterium jeikeium*, Acinetobacter species, polymicrobial organisms, atypical mycobacteria, and multidrug resistant organisms or fungemia due to Candida species.

Empiric antifungal therapies with azoles or echinocandins should be considered in those with high risk of invasive fungal disease or persistent fever despite prolonged (≥4 days) antibiotic therapy and anticipated duration of neutropenia (≥10 days) in consultation with an infectious disease specialist.

Crystalloid fluid resuscitation should be judicious and must be guided by clinical response and age-specific hemodynamic parameters. These patients are at high risk of fluid overload, acute lung injury, circulatory overload, cardiac failure, capillary leak syndrome, and multiorgan dysfunction. Excessive crystalloid only resuscitation can lead to hypoalbuminemia, hyperchloremic metabolic acidosis, and dilutional anemia, which can worsen an ongoing capillary leak syndrome and multiorgan dysfunction. Therefore, many experts are now recommending early initiation of vasopressor infusions along with the use of colloids to minimize these complications. However, current evidence is limited in support of such practice. Many children with cancer have absolute or relative adrenal insufficiency due to anticancer therapies, recent steroid use, and/or cranial radiation exposure. Timely supplementation of hydrocortisone is strongly recommended in those with fluid-refractory, catecholamine-resistant septic shock, and suspected or proven adrenal insufficiency. Cytokine release syndrome, postengraftment syndrome, and secondary HLH syndrome should be suspected in those with HCT or exposure to immunotherapies (e.g., CAR T-cells and monoclonal antibodies). However, the decision to use steroids (methylprednisolone and dexamethasone) to allay cytokine release syndrome, postengraftment syndrome, or secondary HLH should be made in conjunction with the treating hemato-oncology specialist particularly given the propensity of these steroids to produce lymphopenia. A careful evaluation is needed to estimate the risk of graft or CAR T-cell failure in response to steroid therapy versus the risk of worsening organ failure related to immune dysregulation. The use of G-CSF and granulocyte infusions is limited to those with prolonged neutropenia (ANC < 500 cells/μL) and persistent infection despite being on adequate antimicrobial coverage (>48 hours). Although G-CSF has been found to decrease the duration of neutropenia in clinical trials, it has failed to demonstrate benefits in terms of mortality. Currently, routine use of G-CSF is not recommended in severe sepsis or septic shock in immunosuppressed patients.

39.3 Hemophagocytic Lymphohistocytosis Syndrome

The common clinical manifestations of hemophagocytic lymphohistocytosis (HLH) are severe cytopenia, hepatosplenomegaly, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia.

Hemophagocytic lymphohistocytosis (HLH) syndrome is an increasingly recognized life-threating condition of immune dysregulation. The pathogenesis of HLH includes uncontrolled activation of lymphocytes (NK-cells) and macrophages, which leads to the release of proinflammatory cytokines (IFN-γ, TNF-α, IL-6, and M-CSF), an "acute cytokine storm," and a resultant hyperinflammatory state. The common clinical manifestations are severe cytopenia, hepatosplenomegaly, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia. HLH can be classified as primary (inherited mutations) or acquired (infections, autoimmune diseases and primary immune deficiency syndromes). The diagnostic criteria of HLH include clinical, laboratory, and molecular criteria. Clinical manifestations of primary and secondary HLH are similar. The diagnosis of HLH can be made if five out of eight clinical and laboratory criteria are met or any predisposing genetic mutations are identified (Table 39.5). In general, most patients present with high grade, prolonged fever (>1 week), skin rash (30–45% of patients), hepatosplenomegaly, and cytopenia. Late clinical manifestations include liver dysfunction, DIC, seizures, altered mental status, multiple organ failure, and death if the pathophysiology is left unchecked by therapeutic interventions.

39.3.1 Primary HLH

Primary HLH is more frequent in infants, and up to 65–80% of primary HLH patients present within 1 year of age. The majority of primary forms of HLH are caused by mutations in genes encoding proteins for components essential for perforin-dependent T- and NK-cell cytotoxic activity. Thus far, mutations in five of these genes have been identified (Table 39.6). However, newer mechanisms with no, or only partially impaired cytotoxic activity have been elucidated including: (1) partially impaired cytotoxic activity to EBV infection,

Table 39.5 Revised Histiocytosis Society 2004 Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis (HLH)

Diagnosis of HLH can be confirmed if either criterion A or B is fulfilled
(A) Molecular diagnosis consistent with familial or primary HLH (B) Clinical and biochemical criteria for HLH (if at least 5 of 8 criteria are fulfilled below) 1. Fever 2. Splenomegaly 3. Cytopenia (affecting two or more of the three lineages) Hemoglobin concentration < 9.0 g/dL Platelet count <100,000/μL Absolute neutrophil count <1000/μL 4. Hypertriglyceridemia (≥3 mmol/L or ≥265 mg/dL) and/or hypofibrinogenemia (≤1.5 g/L) 5. Elevated ferritin (≥500 μg/L) 6. Evidence of hemophagocytosis in bone marrow, spleen or lymph nodes without evidence of malignancy 7. Low or absent NK-cell activity 8. Soluble CD25 (soluble IL-2 receptor ≥2400 U/mL)
Adapted from: Henter et al. (2007)

Table 39.6 Types and related molecular defects of primary hemophagocytic lymphohistiocytosis (HLH)

Primary HLH type	Syndrome	Gene	Biochemical findings
Impaired cytotoxic granule dependent	FHL2	PRF1	Low or absent perforin expression
	FHL3	UNC13D	Low CD107a expression
	FHL4	STX11	Low CD107a expression
	FHL5	STXBP2	Low CD107a expression
	Griscelli type 2 (hypopigmentation)	RAB27A	Low CD107a expression
	Chediak-Higashi (hypopigmentation)	LYST	Low CD107a expression
Partially impaired cytotoxic activity to EBV infection	XPL1 Duncan's disease	SH2D1A	Low or absent SAP expression, reduced NK- and T-cell activity
Uncontrolled activation of inflammasome	XLP2	BIRC4 NLRC4	Reduced NK- and T-cell activity High IL-18 levels
Severe or impaired T-cell function	Primary immune deficiency syndrome	IL2GR IL7R CD3e RAG-1 ORA1 CD27 ITK	Impaired T-cell activity

Adapted from: Sepulveda and de Saint Basile (2017)
EBV Epstein Barr virus, *SAP* SLAM (signaling lymphocytic activation molecule)-associated protein

(2) uncontrolled activation of inflammasome-associated components, and (3) severe or partial T-cell dysfunction associated with some primary immunodeficiency disorders.

39.3.2 Secondary HLH

Secondary HLH has been associated with several conditions including viral infections (25–30%), bacterial and protozoan infections (20%), malignancies (15–20%), rheumatologic disorders (5–10%), and more recently, biological cancer therapies. Herpes viruses including EBV and Human Herpes Virus-6 (HHV-6) are frequently reported triggers for either primary or secondary HLH. These viruses can infect B-cells and activate the immune system. Secondary HLH is often associated with hematological malignancies such as T-cell lymphoma, B-cell lymphoma, and leukemia, and rarely, solid tumors such as sarcomas and germ cell tumors. Macrophage Activation Syndrome (MAS), often classified as secondary HLH, can be associated with many rheumatologic and inflammatory disorders especially systemic juvenile idiopathic arthritis, Still disease, systemic lupus erythematosus, Kawasaki disease, and

familial Mediterranean periodic fever syndrome. The exact pathophysiologic mechanisms leading to secondary HLH in an individual condition are not fully understood, but an underlying uncontrolled/dysregulated activation of the immune system as the central process has been implicated in most conditions. There is an on-going movement to simply have MAS be considered secondary HLH.

39.3.3 Management of HLH

A high index of suspicion is required to identify children with either primary or secondary HLH. Any patient in the PICU with clinical features of the systemic inflammatory response syndrome and multiorgan dysfunction is a potential case of HLH. It is prudent to obtain supportive biochemical and diagnostic tests in patients who meet the clinical component of the Histiocytosis Society HLH diagnostic criteria (Table 39.5). Therapies to target hyperactive T-cells and histocytes should be promptly initiated if a patient meets HLH diagnostic criteria. For those patients with suspected or proven *primary HLH*, treatment based on HLH-94 or HLH-2004 protocols, which includes a combination of chemotherapy (etoposide and methotrexate) and immunosuppression (dexamethasone and cyclosporine A) is recommended. HLH 94 /2004 includes an 8-week course of etoposide, intrathecal methotrexate, and dexamethasone followed by cyclosporine and pulse doses of etoposide and dexamethasone. Many children with primary HLH require evaluation for hematopoietic cell transplantation. For resistant cases, the use of other investigational therapies including alemtuzumab (anti-CD52), daclizumab (anti-CD25), and infliximab (anti-TNF) has been reported with varying responses.

The treatment of *secondary HLH* remains a matter of discussion. In 2019, recommendations for the management of HLH in adults suggested less aggressive and individualized management based on the underlying etiology for the secondary HLH. Successful use of the IL-1 receptor antagonist (anakinra) for MAS, monoclonal antibodies against B-cell CD20 protein (rituximab) for persistent EBV-induced HLH, and monoclonal antibodies against IL-6 receptor for CAR T-cell induced HLH has been reported.

39.4 Anticancer Therapies

Anticancer therapies are rapidly evolving with a paradigm shift in the approach to cancer. No longer is cancer considered merely a clonal proliferation of transformed tumor cells, but rather, carcinogenesis is viewed as a combination of both proliferation of tumor cells and nontransformed heterogeneous factors including endothelial cells, extracellular matrix, and immune cells. Consequently, anticancer therapies can target DNA by directly disrupting the DNA helix and/or by interfering with DNA-associated proteins. In addition, these therapies can modify the expression of certain genes, inhibit RNA, target cell surface receptors, or intracellular proteins, disrupt components of the extracellular matrix and endothelium, and/or modulate the immune system. Classically, anticancer therapies are divided into groups based on their mechanism of action and chemical structures such as chemotherapy (e.g., alkylating agent, antimetabolite, and topoisomerase inhibitor), hormonal therapy, radiation therapy, and immunotherapy. Recently, a new classification has been proposed and widely adapted in which anticancer therapies are classified based on their target element in the carcinogenesis (Table 39.7). Table 39.7 also

Table 39.7 Common chemotherapy agents used in childhood malignancies

Agent	Used for	Side effects	Special considerations
Directed against DNA			
Alkylating agents			
Cyclophosphamide (toxicity >100 mg/kg cumulative dose)	Lymphoma Leukemia Neuroblastoma Sarcomas	Bone marrow suppression Hemorrhagic cystitis With high dose – SIADH Rare – Hemorrhagic myocarditis, VOD, pulmonary fibrosis	Mesna to prevent cystitis Dialysis for severe overdose
Ifosfamide	Third line-lymphoma, testicular cancer, osteosarcoma and sarcomas	Bone marrow suppression Hemorrhagic cystitis Metabolic encephalopathy Severe nephrotoxicity (glomerular and tubular)	Mesna to prevent cystitis IV methylene blue for severe encephalopathy
Decarbazine	Lymphoma Ewing sarcoma Pheochromocytoma	Severe emesis Hepatitis Hepatic necrosis Hepatic vein thrombosis	Avoid in preexisting liver dysfunction Premedicate with dexamethasone plus 5-HT3 inhibitors
Bleomycin	Lymphoma NHL Testicular cancer	Acute or chronic pulmonary fibrosis Rare cases – ARDS	Exposure to supplemental oxygen increases the risk of lung toxicity
Platinum agents (cisplatin and carboplatin)	Testicular cancer Sarcoma Ovarian	Peripheral neuropathy Sensory neural deafness Bone marrow suppression	Hydration and diuresis to prevent accumulation and minimize toxicity
Directed against DNA-related proteins			
(topoisomerases I and II andetoposide)	Hodgkin lymphoma NHL Leukemia Testicular tumor HLH	Bone marrow suppression Secondary AML	

(continued)

Table 39.7 (continued)

Agent	Used for	Side effects	Special considerations
Antimetabolites			
Antifolate Methotrexate	ALL Osteogenic sarcoma	Mucositis Anemia Bone marrow suppression Encephalitis with intrathecal dose Stroke-like symptoms Acute kidney injury	Folinic acid (Leucovorin) rescue Hemodialysis in severe cases Glucarpidase (new investigational drug)
Pyridimine analogs			
Cytarabine	ALL AML NHL	Bone marrow suppression Subacute noncardiogenic pulmonary edema Mucositis Keratitis	
5-fluorouracil	Breast cancer Colon cancer Stomach cancers	Diarrhea Bone marrow suppression Cardiac dysfunction	
Gemicitabine	Lung cancers, pancreatic and ovarian cancers	Bone marrow suppression Capillary leak syndrome PRES	
Purine analogs			
Mercaptopurine (6-MP)	ALL AML NHL Autoimmune diseases	Hepatitis Pancreatitis Secondary malignancies	
Antitumor antibiotics			
Anthracyclines Dactinomycin Daunorubicin Doxorubicin	Wilms tumor ALL AML Osteogenic sarcoma NHL Neuroblastoma Other childhood sarcomas	Secondary malignancies Cardiomyopathy (cumulative dose >600 ng/m^2 for daunorubicin, >450 ng/m^2 for doxorubcin) Dysrhythmias Heart failure	Drugs with antioxidant properties (dexrazoxane) and carvedilol have been found to decrease cardiac toxicity

Table 39.7 (continued)

Agent	Used for	Side effects	Special considerations
Microtubule inhibitor			
Vinca alkaloids Vincristine Vinblastine	ALL AML Ewing sarcoma Lymphoma Wilms tumor	Bone marrow suppression Peripheral neuropathy (more in vincristine) Alopecia Constipation	Gabapentin for neuropathic pain and glutamine supplementation to prevent peripheral neuropathy have been used
Enzymes			
L –asparaginase	ALL AML	Pancreatitis Hepatitis DIC Anaphylaxis	High risk for deep venous thrombosis
Tumor protein-targeted therapies			
Tyrosine kinase inhibitors			
Imatinib	Philadelphia + AML and CML	Bone marrow suppression Edema Weight gain Congestive heart failure	Cytochrome P450 dependent metabolism Avoid simultaneous use of drugs that can inhibit cytochrome P450
Alisertib	MYCN + Neuroblastoma	Bone marrow suppression Fatigue	

SIADH syndrome of inappropriate antidiuretic hormone, *VOD* veno-occlusive disease, *IV* intravenous, *NHL* non-Hodgkin lymphoma, *ARDS* acute respiratory distress syndrome, *AML* acute myeloid leukemia, *HLH* hemophagocytic lymphohistiocytosis, *ALL* acute lymphoid leukemia, *PRES* posterior reversible encephalopathy syndrome, *DIC* disseminated intravascular coagulation, *CML* chronic myeloid leukemia

includes a few of the side effects of these therapies most relevant to the critical care provider. A detailed discussion of individual antineoplastic medications is beyond the scope of this chapter. However, a few conventional and emerging novel anticancer therapies with relevance to the pediatric critical care provider will be briefly discussed.

39.4.1 Agents Disrupting the DNA Helix

39.4.1.1 Alkylating Agents

Alkylating agents were one of the first class of drugs used for anticancer therapy. They are cytotoxic as alkylation results in disruption of DNA nucleotide sequence, abnormal messenger RNA coding, DNA breakage, and stoppage of DNA replication. The cancer cells are rendered unable to replicate effectively and enter into apoptosis. These agents are effective against actively dividing

cells irrespective of the point in the cell cycle. Therefore, they are cell cycle phase independent. Common alkylating agents include nitrogen mustard (cyclophosphamide, ifosfamide, and chlorambucil), nitrosoureas (carmustine and lomustine), triazenes (decarbazine), antibiotics (bleomycin and mitomycin), and platinum compounds (cisplastin, carboplatin, and oxaliplatin).

39.4.2 Agents Interfering with DNA-Related Proteins

Antimetabolites, topoisomerase inhibitors, and anthracyclines can interfere with DNA–protein complexes without directly binding to DNA. They disrupt DNA production and replication required for cell growth and division.

39.4.2.1 Antimetabolites

Antimetabolites are analogs of various substances including nucleosides, amino acids, or vitamins. They compete with the natural substrates for an active binding site or receptor to inhibit the enzymatic process necessary for replication of cells. These agents are most active during the S-phase of the cell cycle. Also, their efficacy is improved if given over a long period of time. Common antimetabolites often used are antifolates (methotrexate), pyrimidine analogs (cytarabine, 5-fluorouracil, and gemcitabine), adenosine analogs (fludarabine and cladribine), and purine analogs (mercaptopurine (6-MP)).

39.4.2.2 Topoisomerase I and II Inhibitors

Topoisomerase enzymes control the changes in DNA tri-dimensional structure by controlling winding and unwinding of double stranded DNA. Topoisomerase inhibitors include camptothecin derivatives (irinotecan and topotecan) exerting their cytotoxic effect by inhibiting topoisomerase I. Epipodophyllotoxin derivatives (etoposide and teniposide) and anthracyclines (daunorubicin and doxorubicin and their analogs epirubicin and idarubicin) inhibit topoisomerase II.

39.4.3 Antitumor Antibiotics

Antitumor antibiotics are derived from microorganisms. They are usually cell cycle independent agents and are especially useful in slowly growing tumors. They act by several mechanisms including the induction of DNA strand breaks, intercalation between DNA base pairs, and inhibition of topoisomerase II. This family of cytotoxic agents includes anthracyclines (daunorubicin, doxorubicin, liposomal doxorubicin, epirubicin, and idarubicin), bleomycin, mitomycin, and mitoxantrone.

39.4.4 Vinca Alkaloids and Taxanes

These drugs bind to microtubular proteins, thus inhibiting microtubule assembly (M-phase of the cell cycle) and resulting in dissolution of the mitotic spindle structure. They include vinblastine, vincristine, vindesine, and vinorelbine. Taxanes (paclitaxel, docetaxel, and cabazitaxel) not only bind to microtubules, but also promote microtubule assembly and resistance to depolymerization, resulting in the production of nonfunctional microtubules.

39.4.5 Kinase Inhibitors

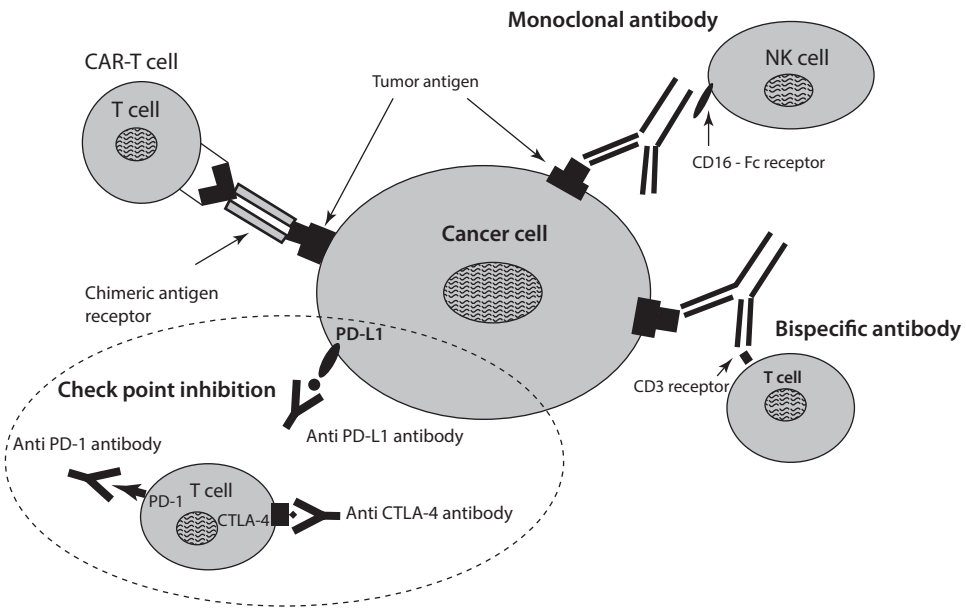
Kinases are a group of catalyst enzymes (>500) involved in phosphorylation in cells. Kinases are composed of a binding site for ATP and one or more sites for substrates. Various types of kinase inhibitors have been developed to inhibit overactive kinases implicated in breast, bowel, lung, and blood cancers. Kinase inhibitors can be classified into direct (reversible and irreversible) or indirect inhibitors. In general, the use of kinase inhibitors is limited in childhood cancers. Examples include imatinib, an intracellular tyrosine kinase (BCR-ABL) inhibitor, used to treat childhood Philadelphia positive acute lymphocytic leukemia and chronic myeloid leukemia; and alisertib, an aurora A kinase inhibitor used in high-risk (MYCN +) neuroblastoma.

39.4.6 Cancer Immunotherapies

Cancer immunotherapy is a novel and emerging anticancer therapy which utilizes and enhances the natural capability of the patient's immune system to eliminate malignant cells. They can be broadly classified into two categories: agents that amplify or modulate natural immune responses (e.g., checkpoint inhibitors) versus agents that are designed to induce new immune responses (e.g., monoclonal antibodies and chimeric antigen receptor (CAR) T-cell) (◘ Fig. 39.5 and ◘ Table 39.8).

39.4.7 Checkpoint Inhibitors

Checkpoint inhibitors activate the patient's own T-cells against cancer by inhibiting checkpoint proteins on the T-cell surface. Three commonly targeted proteins of checkpoint inhibitors are CTLA-4, PD-1, and PD-L1 (◘ Fig. 39.5).



◘ **Fig. 39.5** Common surface protein targets for cancer immunotherapy including checkpoint inhibitors, monoclonal antibody, bispecific antibody and CAR T-cells to treat childhood cancer

Table 39.8 Immunotherapies used for childhood malignancies

Agent	Used for	Side effects
Host immune amplifying or modulating agents		
Checkpoint inhibitors		
Anti-CTLA- 4 antibodies Ipilimumab	Refractory childhood solid tumors Melanoma Small cell lung cancers	Systemic inflammatory reactions Protracted diarrhea Hepatitis Rashes
PD-1 and PD-L1 antibodies Nivolumab Pembrolizumab Atezolizumab	Refractory childhood solid tumors	Systemic inflammatory response Immune-mediated multiorgan dysfunction endocrinopathies Cytokine release syndrome Encephalitis Myasthenia gravis
New immune response to target cancer proteins		
Monoclonal antibodies Dinutuximab (anti-GD2 ganglioside)	Neuroblastoma	Anaphylaxis, sensory-motor neuropathy, capillary leak syndrome, rashes, electrolyte imbalance
Rituximab (anti-CD20 anti-B-cell antibodies)	NHL	Anaphylaxis, immunosuppression, cytokine release syndrome, atypical infections, reactivation of dormant infections, progressive multifocal leukoencephalopathy
Alemtuzimab (anti-CD52 anti-mature B-cell antibodies)	CLL Conditioning for HCT	Anaphylaxis, serum sickness, bone marrow suppression, hepatitis, cytokine release syndrome, opportunistic infections
Bispecific monoclonal antibodies Blinatumomab, (anti-CD3/anti-CD19 bispecific monoclonal antibodies)	Refractory B-cell ALL	Anaphylaxis, serum sickness, bone marrow suppression, hepatitis, cytokine release syndrome, opportunistic infections
Autologous chimeric antigen receptor (CAR) T-cell therapy Tisagenlecleucel	Refractory PreB cell ALL	Cytokine release syndrome, CAR T-cell related encephalopathy syndrome (CRES) and secondary HLH, anaphylaxis, serum sickness Anti-IL-6 antibody and corticosteroids are often used to mitigate the cytokine storm

NHL non-Hodgkin lymphoma, *CLL* chronic lymphoid leukemia, *HCT* hematopoietic cell transplant, *ALL* acute lymphoid leukemia, *HLH* hemophagocytic lymphohistiocytosis

Anti-CTLA-4 antibodies (ipilimumab): CTLA-4 suppresses cytotoxic T-cell and helper T-cell activity by attaching to CD28 and B7 surface receptors, respectively. Thus, CTLA-4 blocking antibodies increase the activity of cytotoxic T-cells and helper T-cells, thereby activating suppressed T-cells, which can recognize and fight cancer cells.

PD-1 and PD-L1: Programmed cell death protein-1 is naturally found in activated T-cells that migrate to the tissue. The main purpose of these proteins

is to limit the duration of T-cell activation and to prevent autoimmune disorders. Commonly used PD-1 and PD-Ligand-1 antibodies include nivolumab, pembrolizumab, and atezolizumab.

Unwanted side effects of checkpoint inhibitors are an increase in severe inflammatory reactions including protracted diarrhea, rashes, and hepatitis. Also, treatment response is highly variable related to the heterogeneity in the patient's immune response to cancer cells, suppression of T-cells by several other checkpoint proteins, and the inability to overcome physical and/or chemical barriers surrounding the cancer cells. Additional agents are often needed to overcome partial resistance to checkpoint inhibitors.

39.4.8 Antibody Therapy

39.4.8.1 Monoclonal Antibodies

Monoclonal antibodies are designed to bind to a specific surface antigen on tumor cells. They induce antibody-dependent cellular cytotoxicity (ADCC) via Fc-receptor mediated activation of NK-cells and macrophages (◘ Fig. 39.5). In childhood cancer, the first immunotherapy to definitively demonstrate clinical benefit was dinutuximab, targeting GD2, a ganglioside overexpressed in neuroblastoma. Adjuvant dinutuximab administered as a part of multimodality regimen including cytotoxic chemotherapy, radiation, and autologous stem cell transplant is now the standard therapy for patients with high-risk neuroblastoma. Rituximab is an anti-B-cell antibody (anti-CD20) now commonly used in the treatment of non-Hodgkin lymphoma. Alemtuzumab is an antibody directed against mature B-cells (anti-CD52) that is used for chronic lymphocytic leukemia and as a preconditioning regimen for HCT.

39.4.8.2 Bispecific Monoclonal Antibodies

Bispecific monoclonal antibodies can simultaneously bind to a specific tumor antigen and activate T-cells in close proximity by connecting to CD3 on the T-cell surface, which results in T-cell directed anticancer activity (◘ Fig. 39.5). Blinatumomab, an anti-CD3/anti-CD19 bispecific monoclonal antibody, mediates significant anticancer effects in CD19-expressing B-cell acute lymphoblastic leukemia (B-ALL).

Common adverse effects of antibody therapy include allergic reactions, serum sickness, anaphylactic shock, cytopenia, hepatitis, cytokine release syndrome, and increased risk of opportunistic infections due to immunosuppression.

39.4.9 Adoptive Therapy

39.4.9.1 Autologous Chimeric Antigen Receptor (CAR) T-Cell Therapy

In 2017, the US Food and Drug Administration approved the first CAR T-cell therapy, tisagenlecleucel, to treat children and young adults with relapsed and/or refractory acute lymphoblastic leukemia (ALL). The emerging data suggest overall remission rates as high as 90% for refractory or relapsed precursor B-cell ALL disease, which had historically very poor cure rates (15–20%). The success of CAR T-cell therapy signifies an important milestone and a paradigm shift in the management of childhood cancers. Recently, the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, Hematopoietic Cell

Transplantation (HCT) – Cancer Immunotherapy Subgroup and the MD Anderson Cancer Center CAR T-Cell Therapy – Associated Toxicity (CARTOX) Program have collaborated to provide comprehensive consensus guidelines on the care of children receiving CAR T-cell therapy. This is an excellent resource for those interested in a more thorough review on CAR T-cell therapy. The following section provides a brief overview of CAR T-cell therapy.

CAR T-cell therapy involves genetic modification of T-cells to express a chimeric antigen receptor specific to a cancer cell antigen. CAR T-cells can be collected either from the patient or by an allogeneic donor. The isolated T-cells are modified via viral transduction or nonviral gene transfer techniques (i.e., DNA-based transposons, CRISPR/Cas9 technology, or direct transfer of *in vitro* transcribed mRNA by electroporation) to express a specific CAR. CARs are fusion proteins consisting of an extracellular antigen recognition domain, a selected single-chain variable fragment (scFv) from a specific monoclonal antibody, linked to an intracellular signaling domain and one or more co-stimulatory domains (Fig. 39.5). The extracellular domain helps in recognition of a specific tumor cell surface antigen (i.e., CD-19) without needing HLA presentation of tumor antigen. The intracellular domains signal T-cell proliferation, cytokine release, and cytolysis to eliminate tumor cells.

CAR T-cell therapy can lead to serious and unique life-threatening adverse effects including cytokine release syndrome (CRS), CAR T-cell related encephalopathy syndrome (CRES), and secondary HLH. Although the pathophysiology of these toxicities is poorly understood, macrophage derived IL-1, IL-6, and nitric oxide have recently been implicated.

39.4.9.2 Cytokine Release Syndrome (CRS)

Cytokine release syndrome (CRS) is the result of a rapid and excessive release of cytokines leading to a severe systemic inflammatory response. The patients with high disease burden, early onset of CRS (within 3 days), and preexisting co-morbidities are more likely to develop severe CRS.

A rapid and excessive release of cytokines leads to a severe systemic inflammatory response. The manifestations vary from isolated fever to shock and multi-organ failure. About two-thirds of patients receiving CAR T-cell therapy develop CRS. The patients with high disease burden, early onset of CRS (within 3 days), and preexisting co-morbidities are more likely to develop severe CRS. The severity of CRS can be graded based on the detailed pediatric specific consensus statement published in *Nature Reviews* (Mahadeo 2019).

The treatment of CRS primarily consists of symptomatic management of organ dysfunction, fluid resuscitation and vasopressors to treat shock, respiratory support ranging from supplemental oxygen to mechanical ventilation based on the degree of respiratory failure, evaluation of infections and empiric antimicrobials, and renal replacement therapy as indicated. Anti-IL-6 antibodies and corticosteroids are often used to counteract cytokine storm. As per the consensus statement, the early use of anti-IL-6 antibodies (e.g., tocilizumab) in patients with persistent or refractory fever and grade 1 CRS or higher is recommended. The use of dexamethasone and low dose methylprednisolone is recommended in patients with grade >/= 3 CRS, and high dose methylprednisolone is indicated in patients with grade 4 CRS, if low dose corticosteroids does not lead to clinical improvement.

39.4.9.3 CAR T-Cell Related Encephalopathy Syndrome (CRES) or Immune Effector Cell Asscociated Neurotoxicity Syndrome (ICANS)

CRES or ICANS commonly presents as delirium, seizures, elevated intracranial pressure (ICP), cerebral edema, and/or toxic encephalopathy. CRES can either occur early on, simultaneously with CRS, or later without associated CRS. Treatment is mainly symptomatic including seizure prophylaxis with medications such as levetiracetam, management of status epilepticus using

continuous electroencephalogram monitoring, advanced ICP monitoring and control by using hyperosmolar therapy and sedation, and dexamethasone and anti-IL-6 antibodies for those with evidence of cerebral edema and severe neurological manifestations.

39.4.9.4 Radiation Therapy

Radiation therapy remains an important component of many anticancer therapies. Up to 30–40% of children receive some form of radiation therapy. The primary mechanism of radiation therapy is to inhibit the multiplication of dividing cells. The ionizing radiation deposits physical energy to cells, which either causes cell death or disrupts the DNA. However, ionizing radiation damages both normal cells and cancer cells. The biological effectiveness (cell killing) of radiation depends on the linear energy transfer, the total dose, the fractionation rate, and the radio-sensitivity of the targeted cells or tissues. Radiation therapy can be delivered by external beam of high-energy rays or by a radioactive catheter placed inside the body (brachytherapy). Types of radiation include photons (X-rays or gamma rays) and particles (electron, proton, and neutron).

Common external radiation therapy machines include the linear accelerator, the CyberKnife, and the Gamma knife. It is important to focus the radiation dose on abnormal cancer cells with all attempts made to minimize the exposure to normal cells, which are adjacent to cancer cells or in the path of radiation. There are many different techniques with varying precision used to give external radiation therapy:

1. Standard external radiation therapy implies the use of a linear accelerator. It is often used to provide a low dose of frequent radiation to the affected body part.
2. Three dimensional (3-D) conformal radiation therapy and 3-D intensity modulation therapy use CT or MRI measurements to obtain the exact location and shape of the tumor mass to provide high dose radiation to the tumor mass.
3. Volumetric-modulation arc therapy can provide a 360° rotational radiation beam to the tumor mass.
4. Stereotactic radiosurgery delivers very precise high dose radiation to the tumor mass in a single session. It is a common technique applied for brain or spinal cord tumors.
5. Whole brain radiation therapy gives radiation to the entire brain.
6. Total body radiation gives radiation to the entire body.

Adverse effects of radiation therapy depend on the intensity of the radiation, the duration of the therapy, and the body parts involved. General adverse effects are fatigue, anemia, radiation dermatitis, alopecia, cytopenia, and loss of appetite. Radiation to brain tissue can cause seizures, cerebral edema, hypopituitarism, cranial nerve palsies, and radiation encephalopathy. Radiation to the chest can cause radiation pneumonitis, dysrhythmia, pericarditis, and restrictive cardiomyopathy. Radiation pneumonitis traditionally occurs 4–12 weeks after the radiation therapy. Thus, it is important for the pediatric intensive care provider to specifically solicit a history of this treatment in oncology patients admitted to the PICU with respiratory failure as the admission will likely not be temporally associated with the radiation therapy. Radiation to the abdomen can cause radiation enteritis, intestinal perforation, and pancreatitis.

Adverse effects of radiation therapy depend on the intensity of the radiation, the duration of the therapy, and the body parts involved.

Radiation pneumonitis traditionally occurs 4–12 weeks after the radiation therapy. Thus, it is important for the pediatric intensive care provider to specifically solicit a history of this treatment as the PICU admission for this condition will likely not be temporally associated with the radiation therapy, and the lung disease may be inappropriately attributed to another etiology.

39.5 Summary

Children with oncological diseases are among the most vulnerable patients in the PICU. These patients have significant morbidity and mortality. The management of these children requires collaborative involvement of many pediatric subspecialities. These patients can present with various critical illnesses ranging from single organ to multiple organ system failure. Their critical illness may be specifically related to their cancer and/or its treatment (e.g., tumor lysis syndrome, hyperleukocytosis, and mediastinal mass) or represent a common critical illness occurring in an at-risk child (e.g., sepsis and pneumonia). Common underlying etiologies include oncological emergencies related to the underlying cancer, toxicities, and adverse effects of anticancer therapies, prolonged immunosuppression, sepsis, hyperinflammatory disorders, and complications of HCT (► Chap. 40).

Review Questions

1. Which of the following metabolic derangements are most commonly associated with tumor lysis syndrome?
   - A. Hypercalcemia, hyperkalemia, hyperphosphatemia, hyperuricemia
   - B. Hypocalcemia, hyperkalemia, hyperphosphatemia, hyperuricemia
   - C. Hypocalcemia, hyperkalemia, hyperphosphatemia, hypouricemia
   - D. Hypocalcemia, hyperkalemia, hypophosphatemia, hyperuricemia
   - E. Hypocalcemia, hypokalemia, hyperphosphatemia, hyperuricemia

2. Which of the following statements most accurately describes the effect of rasburicase?
   - A. It is a prostaglandin analog that increases renal blood flow and thereby enhances uric acid elimination.
   - B. It is a recombinant form of urate oxidase that catalyzes the conversion of uric acid to allantoin.
   - C. It is a recombinant form of xanthine oxidase, the enzyme that augments the conversion of purine nucleic acids into hypoxanthine.
   - D. It is a structural analog of hypoxanthine and functions as a competitive inhibitor of the enzyme xanthine oxidase.
   - E. It is a structural analog of xanthine and functions as a competitive inhibitor of the enzyme urate oxidase.

3. Which of the following is true regarding mediastinal masses in children?
   - A. A brief course of steroids should be started with any radiographic evidence of a mediastinal mass to decrease airway edema and minimize the likelihood of airway obstruction.
   - B. Although data abstracted from the history, physical exam, and radiographic studies may identify patients at increased risk, sedation and anesthesia must be used with great caution in any patient with a mediastinal mass.
   - C. Rapid sequence intubation with deep sedation and neuromuscular blockade is the preferred approach for intubation of the child with a symptomatic mediastinal mass.
   - D. The masses that are most commonly associated with airway obstruction and vascular compression are neural tumors arising in the posterior mediastinum.
   - E. There are no clinical or radiologic findings to assist in identifying patients at increased risk of airway compromise.

4. Which of the following tumors is most likely to arise from the anteriosuperior or middle mediastinum and result in significant cardiopulmonary compromise?
   A. Lymphoma
   B. Myxoma
   C. Neuroblastoma
   D. Rhabdomyosarcoma
   E. Teratoma

5. Which of the following is NOT a risk factor for acute cardiac complications in childhood cancer patients?
   A. Cyclophosphamide
   B. Exposure to mantel radiation
   C. Female gender
   D. Iron overload
   E. Methotrexate

6. Which of the following is a risk factor for posterior reversible encephalopathy syndrome (PRES)?
   A. Cyclosporine A
   B. Hypotension
   C. Maintenance phase of chemotherapy
   D. Older age
   E. Solid tumor

7. A 7 year old child undergoing treatment for acute lymphocytic leukemia presents with temperature of 39.8°, heart rate 172 bpm, respiratory rate 28 bpm, and blood pressure 78/55 mmHg. He is lethargic and has cool extremities with weak peripheral pulses and a 5 second capillary refill time. He has an absolute neutrophil count of 150 cells/μL. Which of the following is the most appropriate antimicrobial therapy?
   A. Cefepime and clindamycin
   B. Cefepime, gentamicin, and vancomycin
   C. Cefepime, vancomycin, and fluconazole
   D. Meropenem and clindamycin
   E. Meropenem and vancomycin

8. A 16 year old male undergoing active treatment for acute myelogenous leukemia presents with persistent relapsing fever, orbital headache, blurry vision and an increase in platelet transfusion requirement. Which of the following is the most likely infection causing the patient symptoms?
   A. *Bacillus cereus*
   B. *Candida albicans*
   C. *Pseudomonas aeruginosa*
   D. *Salmonella typhimurium*
   E. *Staphylococcus aureus*

9. A 13 year old male undergoing active treatment for acute myelogenous leukemia has developed progressive dyspnea with fever and hemoptysis. Computerized tomography of the chest demonstrates a characteristic "halo sign" and bronchoalveolar lavage confirms the diagnosis of Aspergillosis. Which of the following is most appropriate initial antifungal management?
   A. Amphotericin B
   B. Caspofungin

C. Fluconazole
D. Flucytosine
E. Voriconazole

10. Cytokine release syndrome (CRS) has been associated with directed CAR T-cell therapy recently approved to treat relapsed and/or refractory precursor B-cell acute lymphoblastic leukemia. Which of the following agents is used in the management of mild to moderate CRS?
A. Anti-CD20 antibody (rituximab)
B. Anti-IL-6 antibody (tocilizumab)
C. Anti-C5 antibody (eculizumab)
D. Cyclosporine A
E. Methylprednisolone

11. Which of the following is NOT included in the Histiocytosis Society diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH)?
A. Albumin concentration < 3.0 mg/dL
B. Fibrinogen concentration < 1.5 g/L
C. Ferritin concentration ≥ 500 μg/L
D. Hemoglobin concentration < 9.0 g/dL
E. Splenomegaly

Answers

1. B
2. B
3. B
4. A
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Care of the Critically Ill Pediatric Hematopoietic Cell Transplant Patient

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Contents

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Learning Objectives

- To understand the various indications for and the types of hematopoietic cell transplants (HCT) at a level that will provide the pediatric intensive care provider an adequate foundation to care for these children when they develop critical illness.
- To recognize the various etiologies of respiratory failure in the pediatric HCT patient with a focus on those conditions most commonly found in this unique patient population.
- To anticipate the cardiac complications that most commonly occur in the pediatric HCT recipient.
- To understand the clinical manifestations of endotheliopathy in these children with a focus on sinusoidal obstruction syndrome (hepatic veno-occlusive disease) and transplant associated thrombotic microangiopathy.
- To appreciate the high risk of infectious disease in this immunocompromised patient population and to identify common pathogens.
- To appreciate the timing, clinical manifestations and potential treatments for conditions relatively unique to the HCT patient including engraftment syndrome and graft versus host disease.
- To recognize common neurologic emergencies in the pediatric HCT recipient.
- To identify the development of post-transplant lymphoproliferative disease (PTLD) in these high-risk children.
- To understand the role of Chimeric Antigen Receptor (CAR)-Immune Effector Cell Therapy and the potential consequences that may result in critical illness including cytokine release syndrome and CAR T-cell related encephalopathy syndrome (CRES)/immune effector cell associated neurotoxicity syndrome (ICANS).

40.1 Introduction

Hematopoietic cell transplantation (HCT) holds the potential to be a curative therapy for a number of life-limiting malignant and nonmalignant diseases. However, the process is fraught with many risks and life-threatening complications that require critical care services. The ability to effectively prevent and treat these serious complications holds the potential to not only improve outcomes for this most vulnerable patient population but also afford the opportunity to extend this life-saving therapy to other at-risk populations.

In order to most effectively care for these children, the pediatric critical care provider must have a thorough and working understanding of the HCT process. This understanding must include an appreciation for the relationship between the timeline of the HCT process and the most common infectious and noninfectious complications of this treatment. The critical care provider must be able to recognize those life-threatening conditions unique to the HCT patient as well as the presentation of more common critical illnesses in this patient population. It is important to understand that these children not only incur an immunosuppressed state at various stages of the HCT process, but also a dysregulated immune system at other points that may foster uncontrolled inflammation.

In this chapter, the common pulmonary, cardiovascular, and neurologic conditions associated with HCT that result in substantial morbidity and mortality will be reviewed. The clinical manifestations of HCT-associated endotheliopathy including the sinusoidal obstruction syndrome/hepatic veno-occlusive disease as well as transplant associated thrombotic microangiopathy will be described. Conditions relatively unique to the HCT patient such as engraftment syndrome and graft versus host disease (GVHD) will also be reviewed. Finally, the novel

chimeric antigen receptor (CAR) autologous T-cell immunotherapy, now being used to treat refractory or relapsed precursor B-cell acute lymphoblastic leukemia with unprecedented success, will be considered with an emphasis on its unique life-threatening toxicities including cytokine release syndrome and CAR T-cell related encephalopathy syndrome (CRES)/immune effector cell associated neurotoxicity syndrome (ICANS).

40.2 Hematopoietic Cell Transplantation Process

40.2.1 Indications and Types of Transplants

Hematopoietic cell transplantation (HCT) is a potentially curative therapy for a variety of malignant and nonmalignant conditions. Autologous HCT refers to the infusion of a patient's own previously collected stem cells following high-dose chemotherapy. To optimize stem cell collection, patients typically undergo stem cell mobilization and apheresis early in their treatment course (prior to heavy cumulative marrow toxic therapy). The cells are then cryopreserved. Later, high-dose consolidation chemotherapy used to treat the primary disease ablates the marrow (myeloablative therapy) and autologous HCT facilitates hematopoietic recovery. As depicted in ◘ Table 40.1, autologous HCT is used in a variety of high-grade solid tumors.

Different graft sources are associated with varying times to achieve post-HCT hematopoietic recovery and may be associated with infections and other morbidities.

Allogeneic HCT refers to the infusion of hematopoietic stem cells (HSCs) from an either related or unrelated donor source. Indications for allogeneic HCT include high-risk leukemias, bone marrow failure syndromes, and nonmalignant genetic diseases (◘ Table 40.1). Allogeneic HCT for solid tumors is currently under investigation. For malignant diseases, new allogeneic donor hematopoietic cells facilitate a graft-versus-tumor (GvT) effect which may enhance long-term cure rates. In nonmalignant diseases, allogeneic donor hematopoietic cells either directly replace the patient's own hematopoietic cells to cure their primary disease (e.g., primary immune deficiencies and hemoglobinopathies) or cross-correct enzyme deficiencies in neighboring cells and thereby attenuate manifestations of genetic diseases. Donor sources may be classified based on histocompatibility (human leukocyte antigen (HLA) match) and relation to the recipient (◘ Table 40.2). Different graft sources are associated with varying times to achieve post-HCT hematopoietic recovery and may be associated with infectious and other morbidities (◘ Table 40.3).

The primary indication for HCT may pose special management considerations that should be recognized. For example, patients with sickle cell anemia (SCA) undergoing HCT require reduction in their hemoglobin S percent prior to initiation of preparative regimens to avoid sickle cell crises and multiorgan dysfunction. Further, patients with SCA require vigilant monitoring for posterior reversible encephalopathy syndrome (PRES) and require ongoing seizure prophylaxis while receiving calcineurin inhibitor graft-versus-host-disease (GVHD) prophylaxis/treatment. Patients with SCA may have lower baseline blood pressure compared to the general population, so it is important that relative hypertension be recognized. Patients with acute lymphoblastic leukemia (ALL) and adrenoleukodystrophy (ALD) should be particularly monitored for adrenal crisis as they may require stress dose corticosteroid administration during illness. Patients with Hurler syndrome may present with cardiomyopathy requiring careful selection of medications when hypertension is present. These patients may also present with difficult airways, have obstructive sleep apnea, and increased intracranial pressure.

Table 40.1 Indications for allogeneic and autologous hematopoietic cell transplant

Allogeneic		Autologous
Nonmalignant diseases	**Malignant diseases High risk/relapsed or refractory disease**	
Hereditary bone marrow failure syndromes Fanconi anemia Blackfan-Diamond anemia Severe aplastic anemia Dyskeratosis congenita Congenital amegakaryocytic thrombocytopenia Severe congenital neutropenia Shwachman Diamond anemia	*Leukemia* AML ALL APML CML MDS JMML	*Solid tumors* Germ cell tumor Ewing sarcoma Neuroblastoma Wilms tumor Medulloblastoma
Immunodeficiencies SCID Wiskott-Aldrich syndrome Severe congenital neutropenia CGD IPEX *Hemoglobinopathies* Sickle cell disease Thalassemia *Inherited metabolic conditions* Mucopolysaccharidosis Metachromatic leukodystrophy	*Lymphoma* Burkitt lymphoma Hodgkin lymphoma Anaplastic large cell lymphoma B-cell non-Hodgkin lymphoma T-cell non-Hodgkin lymphoma	*Lymphoma* Burkitt lymphoma Hodgkin lymphoma Anaplastic large cell lymphoma Diffuse large B-cell lymphoma
Other Osteopetrosis Adrenoleukodystrophy Hemophagocytic disorders	*Other* MDS	

Adapted from: Majhail et al. (2015) and Sureda et al. (2015)
SCID severe combined immunodeficiency, *CGD* chronic granulomatous disease, *IPEX* immunodysregulation polyendocrinopathy enteropathy X-linked, *AML* acute myelocytic leukemia, *ALL* acute lymphocytic leukemia, *APML* acute promyelocytic leukemia, *CML* chronic myelocytic leukemia, *MDS* myelodysplastic syndrome, *JMML* juvenile myelomonocytic leukemia

40.2.2 Conditioning (or Preparative) Regimens

In autologous HCT, marrow toxic high-dose myeloablative conditioning/preparative regimens used to treat the primary malignancy require stem cell rescue to restore normal hematopoiesis. With few exceptions, conditioning/preparative regimens are used prior to allogeneic HCT. The regimen may consist of chemotherapy with or without radiation and/or serotherapy (e.g., alemtuzumab or antithymocyte globulin) and facilitates tumor burden reduction (in malignant conditions) and adequate immunosuppression for engraftment of the donor hematopoietic stem cells.

Preparative regimens may be classed as myeloablative (MAC), nonmyeloablative (NMA), or reduced intensity conditioning (RIC). Myeloablative regimens consist of alkylating agents with or without high dose total body irradiation (TBI) causing irreversible or near irreversible pancytopenia and require stem cell rescue to restore marrow function. Nonmyeloablative regimens are used primarily to achieve adequate immunosuppression because bone marrow ablation is not neces-

Table 40.2 Types of autologous and allogeneic hematopoietic cell transplants and their donor sources

Type of transplant		Donor source
Autologous		Patient's own hematopoietic stem cells
Allogeneic	Syngeneic	Identical twin donor
	HLA identical sibling/ family donor	10/10 or 8/8 HLA match Umbilical cord blood unit (4/6, 5/6, 6/6 HLA match)
	Matched unrelated donor	Unrelated person (via donor registry) 10/10 or 8/8 match Umbilical cord blood unit (4/6, 5/6, 6/6 HLA match)
	Related haploidentical donor	Family member with one HLA haplotype genetically identical with patient
	Mismatched unrelated donor (mMUD)	Unrelated person (via donor registry) where there is mismatch in HLA

Adapted from: Majhail et al. (2015) and Sureda et al. (2015)
HLA human leukocyte antigen

sary to achieve adequate donor engraftment (usually based on the primary transplant indication). Preparative regimens that do not adequately fall into either of these categories are typically classed as reduced intensity (or reduced toxicity) conditioning regimens. More intense preparative regimens may be associated with a higher risk of endothelial damage and varying rates of associated morbidities such as sinusoidal obstruction syndrome (SOS)/hepatic veno-occlusive disease (VOD), transplant associated thrombotic microangiopathy (TA-TMA), interstitial pneumonitis, idiopathic pulmonary fibrosis, reduced pulmonary function, and renal injury. The choice of specific preparative regimen typically depends on the recipient's age (avoid TBI in children <3 years), primary disease, co-morbidities, and risk of graft failure/rejection.

40.2.3 Timeline

All HCT recipients undergo a comprehensive medical clearance prior to the initiation of the preparative regimen. This entails a detailed medical history including a review of prior treatments as well as assessments of the performance score (Lansky/Karnofsky), organ function, and the co-morbid conditions. The infusion of the HSCs follows administration of the preparative regimen. Infectious prophylaxis, isolation precautions, and transfusion support are typically required until the recipient achieves hematopoietic recovery. Neutrophil engraftment is defined as the first of three consecutive days following HCT with an absolute neutrophil count (ANC) of more than 500/μL. This usually occurs 2–4 weeks after HCT dependent upon the stem cell source (Fig. 40.1). Red blood cell and platelet recovery usually follow thereafter. Complete immune reconstitution (in particular humoral immunity) may only occur months to years following HCT.

Table 40.3 Comparison of the currently used graft sources

Graft source	Availability and collection	$CD34^+$ cells/kg typically present	Time to achieve hematopoietic recovery	Incidence of GVHD
Bone marrow	Requires time for donor medical clearance	Intermediate	Intermediate	Intermediate
	Collection may be limited by donor weight in relation to recipient weight			
	Future donor lymphocyte infusion (DLI) possible			
Peripheral blood	Requires time for donor medical clearance	Greatest	Fastest	Greatest
	Requires stem cell mobilization prior to collection			
	Typically, able to achieve higher cell dose collection/kg of recipient weight			
	Future DLI possible			
Umbilical cord blood	Rapidly available (no medical clearance needed)	Lowest	Slowest	Lowest
	Future DLI not standardly available			

Adapted from: Majhail et al. (2015), Sureda et al. (2015), and Gluckman (2011)
GVHD graft versus host disease

40.3 Respiratory Complications Post-HCT

Pulmonary complications post-HCT are very common and are a significant source of nonrelapse mortality. Between 17% and 44% of HCT children will require critical care services, with respiratory failure being the leading cause for pediatric intensive care unit (PICU) admission.

The etiologies for respiratory failure in this population are diverse. Unfortunately, all etiologies can result in severe respiratory failure, leading to invasive mechanical ventilation. Although the mortality of intubated pediatric HCT patients has improved over time, currently reported mortality rates still discouragingly range between 40% and 60%. Respiratory complications post-HCT can be categorized into infections and noninfections. The diverse etiologies of pulmonary complications render identification and treatment challenging. The testing for infectious sources is imperfect, and many of the noninfectious complications

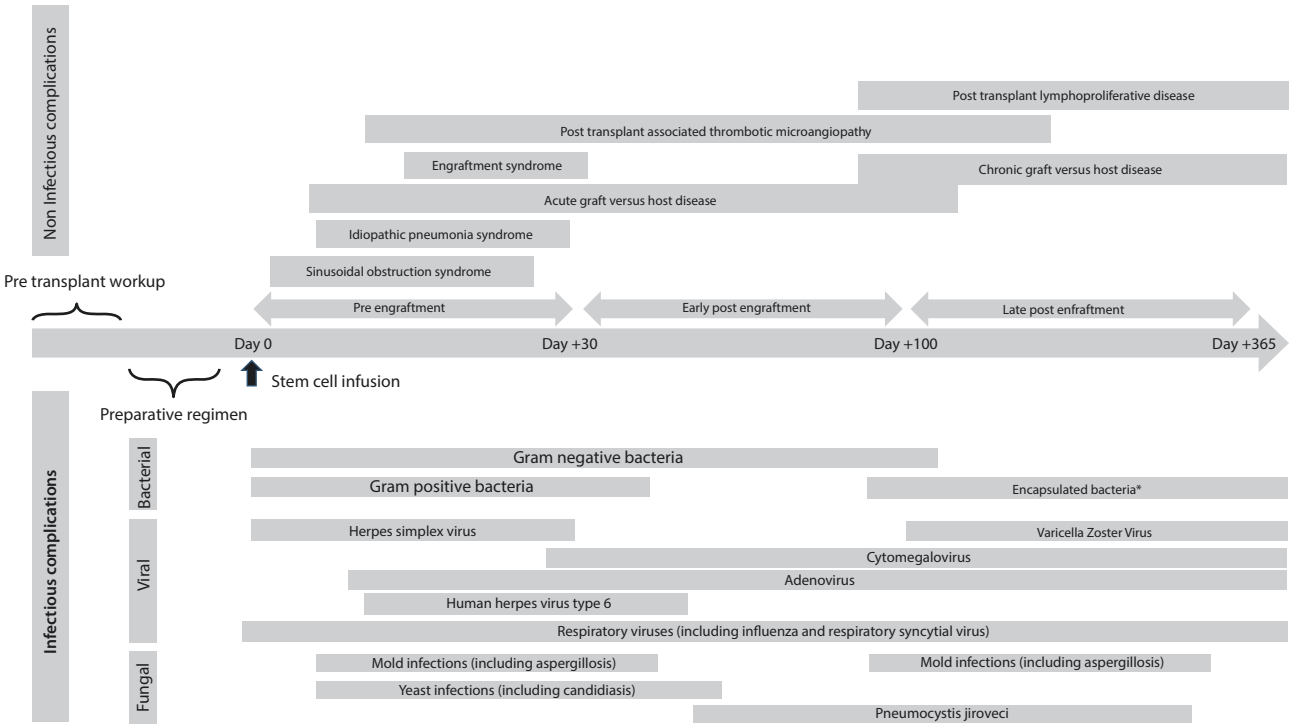

Fig. 40.1 Timeline of common infectious and noninfectious conditions following hematopoietic cell transplant (HCT). The figure depicts the timeline of common infectious and noninfectious conditions following HCT. The periods of HCT are illustrated just above the timeline for a frame of reference. Infectious complications are included below the timeline while noninfectious conditions are illustrated above the timeline. * includes pneumococcus and hemophilus

are based primarily on a constellation of clinical symptoms and/or remain a diagnosis of exclusion.

40.3.1 Infectious Complications

The stage of immune reconstitution affects which pathogens are most likely to cause respiratory infection. The early, preengraftment phase is dominated by common pathogens such as gram-negative and gram-positive bacteria as well as candida. During the periengraftment period, viruses and opportunistic fungi become more prevalent. Encapsulated bacteria and viruses occur most commonly in the postengraftment phase.

The HCT patient is at significantly increased risk for pulmonary infections post-transplant. Lower respiratory tract infections account for up to 50% of all pulmonary complications in children post-HCT. The early, preengraftment phase is dominated by infections secondary to common pathogens including gram-negative and gram-positive bacteria as well as candida. During the periengraftment period, viruses and opportunistic fungi become more prevalent. This is followed by a concern for encapsulated bacteria and viruses in the postengraftment phase (Fig. 40.1).

The diagnostic approach to pulmonary disease in this patient population varies from center to center with the need for bronchoscopy and bronchoalveolar lavage spawning debate. The data surrounding the value of bronchoscopy in the general immunocompromised patient are conflicting with diagnostic yield reports varying between 27% and 85%. However, reports suggest that there is a 20% decrease in mortality if the diagnosis results in a change in therapy. Conversely, the risk of complications with bronchoscopy remains a concern with an incidence as high as 30% in children being reported. Although one study cited less than 1% risk of a new mechanical ventilation requirement following bronchoscopy among the immunocompromised, the risk seems to be higher in HCT recipients. While concerns for complications may result in a

delay, it is important to note that the earlier the bronchoscopy is performed in the disease course, the better the diagnostic yield and the less the risk of complications.

40.3.2 Noninfectious Complications

Noninfectious pulmonary complications following HCT are relatively common, and present a challenge to diagnosis and treatment.

Noninfectious pulmonary complications are challenging and many of them are poorly understood. The diagnosis is often one of exclusion and there are very little treatment options outside of supportive care and corticosteroids. However, progress is being made. There is continued investigation into many of these respiratory problems and new exciting therapies are being assessed and implemented. Collaborative, multicenter studies are needed to further define diagnostic criteria of each specific disease and to optimize possible therapeutic strategies. Several noninfectious complications, organized by general timing of onset, are highlighted in Table 40.4 (Fig. 40.1).

The approach to respiratory support must be considered differently in this patient population than for other critically ill pediatric patients. The risk for both unusual infectious and noninfectious complications in these children often creates a diagnostic challenge. Additionally, there is often a unique opportunity for early intervention as they are frequently hospitalized at the time of respiratory illness development. Moreover, the children post-HCT who develop respiratory illness have a very high risk of developing severe pediatric acute respiratory distress syndrome (PARDS) irrespective of the underlying cause of pulmonary dysfunction. One multicenter study of intubated children post-HCT reported that 92% developed PARDS within the first week of invasive mechanical ventilation. Finally, mortality is exceedingly high among these patients with published mortality rates ranging between 40% and 60%.

The approach to respiratory support for these children is highly variable with little supporting data. Therefore, care is often based on the extrapolation of data from other adult immunocompromised populations and best clinical judgement. One of the most difficult clinical decision points in this population is the timing of intubation. With the exceedingly high mortality rate, clinicians are often hesitant to intubate, opting instead to attempt noninvasive measures. However, emerging data suggest that spending a longer time in respiratory distress prior to intubation results in higher mortality for these children; nonsurvival among this patient population has been reported to be associated with longer lengths of PICU stay prior to intubation, increased use of noninvasive ventilation prior to intubation, and with receiving supplemental oxygen for a week prior to intubation.

In terms of specific forms of respiratory support, there are very little data regarding the use of high flow nasal cannula (HFNC) specific to the pediatric HCT recipient. In a randomized control trial (RCT) of HFNC versus face mask oxygen among 100 immunocompromised adults, there was no difference in the rate of intubation or the work of breathing. In another study of 127 immunocompromised adults, HFNC did not decrease the mortality nor reduce the need for intubation when compared to face mask oxygen. A smaller Japanese study found an 80% failure rate of HFNC among 56 adults with hematological disease. Although there are limited data specific to the pediatric HCT population, HFNC does not seem to be effective in preventing intubation among these patients. Moreover, in utilizing HFNC for this patient population, it is important to remember that data suggest delaying intubation is associated with worse outcomes for these children.

The data for noninvasive ventilation (NIV) are potentially more promising. In an RCT of 40 adults following solid organ transplant, the use of NIV over

Table 40.4 Noninfectious pulmonary complications post-hematopoietic cell transplant (HCT)

Disease process	Definition and incidence	Clinical manifestations and risk factors	Diagnostic findings	Specific treatment
Early complications (within 100 days post-HCT)				
Diffuse alveolar hemorrhage (DAH)	Bleeding in multiple different alveoli creating respiratory distress following HCT	Often occurs with the engraftment of stem cells Respiratory distress Fever Hemoptysis can occur, but is NOT common	Diagnostic criteria: 1. Evidence of widespread alveolar damage 2. Absence of infection 3. Bronchoscopy findings of: Increasing bloody return from three different bronchi > 20% hemosiderin laden macrophages, or Blood in at least 30% of alveolar surface	Supportive care High dose corticosteroids
Periengraftment respiratory distress syndrome (PERDS)	Systemic capillary leak resulting from the graft interacting with the host immune system	Fever Weight gain Diffuse rash Pulmonary edema Hepatic dysfunction Renal dysfunction Encephalopathy	No specific diagnostic criteria, but usually occurs during neutrophil engraftment	Supportive care Controlling fluid balance Corticosteroids
Early or late complications				
Pulmonary cytolytic thrombi (PCT)	Fever and pulmonary nodules that demonstrate necrotic, basophilic thromboemobli on biopsy	Fever Cough Often coincides with GVHD	Pulmonary nodules on chest CT imaging	Corticosteroids Cyclosporine
Idiopathic pneumonia syndrome (IPS)	A wide spectrum of disease processes (many experts believe IPS encompass many of the other noninfectious complications listed on this table).	Cough, tachypnea, dyspnea Negative infectious work up	Evidence of widespread alveolar damage with no identified infection, cardiac dysfunction, acute renal failure, or fluid overload Restrictive PFT findings	Supportive care Corticosteroids Etanercept
Transplant associated thrombotic microangiopathy (TA-TMA)	Systemic endothelial dysfunction that can affect multiple organs including the lungs. Arterioles and capillaries are damaged with thickened walls and lumens obstructed by thrombi. Incidence is highly variable but reported to be as high as 20–30%	It can be mild to severe Pulmonary hypertension Multiorgan involvement particularly in the kidney It can be precipitated by immunosuppressive agents (i.e., calcineurin inhibitors)	Multiple various definitions, but common themes: Elevated LDH New or worsening thrombocytopenia Schistocytes on peripheral smear	Supportive care Discontinuing calcineurin inhibitors Eculizumab for severe cases

Late complications (after 100 days post-HCT)				
Bronchiolitis obliterans syndrome (BOS) and chronic GVHD of the lungs	Progressive airway obstruction that results from fibrosis of the terminal airways and bronchioles; a 2005 NIH consensus reported this is chronic GVHD. It is reported to be one of the most common late pulmonary complications with an incidence ranging from 2% to 26%.	Insidious onset of respiratory symptoms including cough, wheeze, and dyspnea Hyperinflation Often afebrile History of recurrent respiratory infections GVHD in other organs Occurs most commonly in allogeneic HCT	Exclusion of infection and consistent lung biopsy OR Obstructive findings on PFT (FEV_1/FVC < 0.7 and FEV_1 < 75% predicted) and CT findings of air trapping with small airway thickening and bronchiectasis	Corticosteroids first-line therapy; burst followed by a long taper over a year Cyclosporine or tacrolimus Azithromycin Etanercept FAM therapy: Fluticasone, azithromycin, and montelukast
Cryptogenic organizing pneumonia (COP); historically known as bronchiolitis obliterans organizing pneumonia (BOOP)	Involves the bronchioles and distal air spaces. Progressive filling of the alveoli and lumens of the terminal bronchioles with granulation tissue. There is extensive inflammation of the lungs, but no fibrosis.	Fever Cough Dyspnea	Exclusion of infection CT findings of diffuse airspace disease Biopsy with patchy distribution (often peribronchiolar) of fibroblasts/myofibroblasts that involve both alveoli and alveolar ducts, intraluminal fibrosis in distal airspaces Restrictive PFT findings	Corticosteroids, burst followed by long taper
Pulmonary veno-occlusive disease (PVOD)	Rare form of pulmonary hypertension likely a result of endothelial damage	Initially asymptomatic Progressive dyspnea Hypoxia Signs of right heart failure (i.e., peripheral edema, hepatomegaly, and pleural effusions)	Echocardiographic findings consistent with pulmonary hypertension CT findings of ground glass opacities, septal thickening, and mediastinal lymphadenopathy	Supportive care Caution and increased monitoring with pulmonary vasodilators due to a high risk of significant, fatal, pulmonary edema Defibrotide and N-acetylcysteine have unclear benefit

GVHD graft versus host disease, *CT* computed tomography, *PFT* pulmonary function testing, *LDH* lactate dehydrogenase

supplemental oxygen alone was associated with an improvement in oxygenation, a decreased intubation rate (20% vs. 70%) and improved mortality (20% vs. 50%). Similar findings were demonstrated in another RCT of 52 immunocompromised adults. Additionally, a small study of 40 adults with hematologic malignancies found that those randomized to early continuous positive airway pressure (CPAP) had a decrease in the need for intubation and intensive care unit transfer. However, the most recent and largest study had less encouraging results. In that multicenter RCT of NIV versus supplemental oxygen in 374 immunocompromised adults, there was no difference in the rate of intubation, the duration of mechanical ventilation, and the length of stay or survival. In children, a retrospective review of pediatric oncology patients found a 26% failure rate of NIV with hemodynamic instability being a significant risk factor for failure. In a recent multicenter review of intubated pediatric HCT patients, 41% received NIV prior to intubation and those that did had an increased risk of PICU mortality (OR, 2.1; 95% Confidence Interval (CI), 1.2-3.6; $p = 0.01$). Overall, the usefulness of NIV in the pediatric HCT patient remains to be established. Although there may be a potential benefit, NIV would not appear to be indicated in the hemodynamically unstable patient. Additionally, and similar to HFNC, NIV must be implemented within the context of data suggesting delayed intubation is associated with worse outcomes for these children.

Given the significant risk of developing PARDS in the HCT recipient, invasive mechanical ventilation should be implemented with a considerable focus on lung protective strategies. Among these children, data demonstrate an association with increasing peak inspiratory pressures (particularly >31 cmH_2O) and higher mortality, suggesting a need to limit peak pressures below this level. Additionally, there is evidence suggesting these patients may benefit by limiting the fraction of inspired oxygen (FiO_2) and employing a high peak end expiratory pressure (PEEP)/low FiO_2 strategy. In a cohort of 222 pediatric HCT patients receiving mechanical ventilation, those who were treated in a manner compliant with the ARDSnet high PEEP/low FiO_2 strategy at 24 hours of ventilation had improved survival. Further, data suggest that the oxygenation index (OI) is useful for identifying patients at increased risk of mortality in this population.

The value of high frequency oscillatory ventilation (HFOV) in this population is also unestablished. One single center study of immunocompromised children found that those who had improved oxygenation at 24 hours of HFOV were more likely to survive. In another retrospective, twelve center study that included 85 pediatric HCT patients, an earlier transition to HFOV from conventional ventilation was associated with improved survival with survivors being transitioned at a lower OI and earlier in the course of conventional ventilation. In that study, no one survived after being transitioned to HFOV after 1 week of conventional ventilation. In addition, overall survival was poor among the cohort transitioned to HFOV at only 23.5%.

40.4 Cardiovascular Complications Post-HCT

The two most common acute cardiac complications observed in the pediatric HCT population are arrhythmias and cardiomyopathy/cardiac dysfunction.

Cardiac complications can occur in children following HCT. The two most common acute complications observed in this population are arrhythmias and cardiomyopathy/cardiac dysfunction. Hypertension is also a significant cardiovascular concern, and may be associated with the PRES, which is discussed in the neurologic complication section.

Arrhythmias have been reported to occur in 8–11% of children following HCT. It is an early transplant complication with the majority of arrhythmias occurring within the first 100 days post-HCT. The data describing the occur-

rence, types, and specific therapies for arrhythmias in children post-HCT are scarce, and thus, most knowledge is extrapolated from the adult literature. Although pediatric data are sparse, children with arrhythmias post-HCT are more likely to be admitted to the ICU and have a higher mortality. Therefore, it is important for the pediatric intensive care practitioner to have a sound knowledge of this complication. In adults, arrhythmias such as atrial fibrillation, atrial flutter, and supraventricular tachycardia are the most common to affect this population. In a small, single center study of children undergoing HCT, three of the 40 patients experienced nonsustained ventricular tachycardia; all of these patients were asymptomatic. Risk factors for arrhythmias include exposure to anthracycline-based chemotherapeutic regimens and having received thoracic or total body irradiation. In the acute setting, treatment for these symptomatic or hemodynamically compromising arrhythmias is no different than the standard approach for any patient.

Cardiac dysfunction, particularly left ventricular dysfunction, is a well-known, but rare complication found in children undergoing HCT. The dysfunction can occur both at the time surrounding transplantation and as a long-term sequela following HCT. A large study noted that less than 1% of adult HCT patients had a significant, life-threatening cardiac complication within the first 100 days. In a smaller pediatric study of 40 patients, four (10%) developed heart failure. All four children improved. Risk factors for adults have been established and include age and general cardiovascular health. As with arrhythmias, major risk factors for cardiomyopathy and heart failure include anthracycline treatment and radiation therapy. Cyclophosphamide is also known to cause heart failure, particularly at higher doses, secondary to necrosis of myocardial cells. GVHD involving the heart has also been described as a source of cardiac toxicity. Critical care of the HCT patient with heart failure is generally the same as that of any patient with heart failure. Specific care for the HCT patient requires careful monitoring and follow up for long-term cardiac complications.

40.5 Endotheliopathies Post-HCT

40.5.1 Sinusoidal Obstruction Syndrome (SOS)

Sinusoidal obstruction syndrome (SOS), previously known as hepatic veno-occlusive disease (VOD), is a potentially life-threatening complication that can occur in up to 30% of pediatric patients undergoing HCT.

The underlying pathophysiology is likely due to toxins generated by the conditioning regimen, which cause cytokine-mediated inflammation and a procoagulable state, that ultimately result in damage to the sinusoidal endothelial cells and hepatocytes of zone 3 of the hepatic acini. Clinically, this results in decreased hepatic outflow which can lead to portal hypertension, fluid retention, polyserositis due to capillary leak syndrome, tender hepatomegaly, coagulopathy, multiorgan failure, sepsis, and death.

Risk factors for the development of SOS can be divided into preexisting, pre- and post-HCT factors (Table 40.5). It most commonly occurs within 30 days post-transplant (although late onset SOS has been reported). Historically, VOD was characterized by the clinical triad of right upper quadrant pain, weight gain, and an elevated serum bilirubin level as outlined in the Seattle, Modified Seattle and Baltimore criteria. However, given that up to 30% of pediatric patients remain anicteric, the pediatric SOS criteria were updated by the European Group for Blood and Marrow Transplantation (EBMT) and published in 2017 (Table 40.6).

Sinusoidal obstruction syndrome (SOS), previously known as hepatic veno-occlusive disease (VOD), is a potentially life-threatening complication that can occur in up to 30% of pediatric patients undergoing HCT.

Table 40.5 Risk factors for developing sinusoidal obstruction syndrome

Preexisting risk factors	Pre-transplant factors	Post-transplant factors
Age: < 1 year	Total body irradiation	Type of transplant: Allogeneic transplant Matched unrelated donor Multiple sequential autologous transplant Non T-cell depleted transplant
Poor performance status	Treatment with these medications: Cyclophosphamide Busulfan Melphalan Gemtuzumab Ozogamicin	Use of concomitant drugs that cause cholestasis: Cephalosporins Progestogens Azole antifungals Calcineurin inhibitors Methotrexate
Preexisting hepatic dysfunction: Hepatitis Iron overload Prior TPN use		Use of sirolimus with concurrent use of calcineurin inhibitors
Prior myeloablative HCT		
Osteopetrosis		
Underlying disease: Familial HLH JMML		

TPN total parenteral nutrition, *HCT* hematopoietic cell transplant, *HLH* hemophagocytic lymphohistiocytosis, *JMML* juvenile myelomonocytic leukemia

The diagnosis of SOS remains a clinical one and there are no specific or sensitive biomarkers or imaging criteria that are pathognomonic. Keen clinical suspicion is critical as early diagnosis and specific intervention may improve outcomes.

The findings of reversal of blood flow in the hepatic veins, a hepatic artery resistance index greater than 0.75 and/or an abnormal portal vein waveform on doppler ultrasonography of the liver are all supportive of a diagnosis of SOS; however, none are confirmatory, and when found, are typically late findings. Trans-jugular liver biopsy with a pressure gradient of 10 mmHg is highly specific (91%) for SOS in adults. However, due to the high risk of complications and lack of pediatric correlative evidence, this procedure is generally avoided in children, with consideration primarily given when late-onset SOS is suspected to assist with the more elusive diagnosis.

SOS can vary widely in severity from mild to severe with 25% of patients having severe disease. The mortality also varies ranging from 9% in mild cases up to 75–98% in severe disease (Table 40.7). Severe VOD requires PICU care and is associated with renal failure (54%), pulmonary failure (23%), cardiac failure (63%), changes in mental status (78%), multiorgan failure (30–60%), sepsis, and death.

Table 40.6 Diagnostic criteria for sinusoidal obstruction syndrome

Seattle criteria	Modified Seattle criteria	Baltimore criteria	EBMT criteria
Two or more of the following within 30 days post-HCT: – Bilirubin ≥2 mg/dL – Hepatomegaly, RUQ pain – Ascites with/without unexplained weight gain >2% over baseline	Two or more of the following within 20 days post-HCT: – Bilirubin >2 mg/dL – Hepatomegaly or RUQ pain – Unexplained weight gain > 2% over baseline	Bilirubin ≥2 mg/dL and two or more of the following within 21 days post-HCT: Hepatomegaly (usually painful) Ascites Weight gain >5% over baseline	Two or more of the following (no limitation for time of onset): – Rising bilirubin above baseline on three consecutive days or bilirubin ≥2 mg/dL – Hepatomegaly above baseline – Ascites above baseline – Weight gain >5% above baseline or otherwise unexplained weight gain on three consecutive days despite the use of diuretics – Unexplained consumptive and transfusion refractory thrombocytopenia

HCT hematopoietic cell transplant, *RUQ* right upper quadrant, *EBMT* European Group for Blood and Marrow Transplantation

Table 40.7 Grades of severity of sinusoidal obstruction syndrome

	Mild	Moderate	Severe
Persistent, refractory thrombocytopenia	<3 days	3–7 days	>7 days
Elevated transaminases (ALT, AST)	≤2 × ULN	>2 and ≤5 × ULN	>5 × ULN
Bilirubin (mg/dL)	<2	<2	≥2 Rate of rise: Doubles in 48 hours
Ascites	Minimal	Moderate	Parecentesis needed
Coagulation	Normal	Normal	Impaired
Glomerular filtration rate mL/min	60–89	30–59	≤29
Oxygen requirement	≤2 L/min	>2 L/min	Invasive pulmonary ventilation

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *ULN* upper limit of normal

Early initiation of specific therapy with defibrotide in severe SOS may positively impact outcomes. This drug is a polydeoxyribonucleotide that acts locally in the hepatic region (with minimal systemic anticoagulation effect) and has anti-ischemic, antithrombotic, and anti-inflammatory properties. The recommended pediatric dose is 25 mg/kg/day intravenously divided every 6 hours. Treatment duration is 21 days or until there is resolution of multiorgan dysfunction and SOS whichever is longer.

The Bearman model suggests that rapid weight gain is associated with poorer outcomes among patients with SOS. Goldstein et al. reported universal mortality among pediatric HCT recipients with acute renal failure and acute fluid overload who were unable to restore euvolemia. Fluid restriction, inclusive of blood products and medications, and controlled diuresis (potentially with albumin infusion if the serum albumin level is <3 g/dL) as needed to maintain euvolemia is recommended for patients with SOS. Renal replacement therapy is indicated in patients with worsening fluid overload despite conservative measures and for patients with electrolyte abnormalities. Paracentesis may be considered if there is failure to respond to conservative management, intra-abdominal hypertension/compartment syndrome, or cardiopulmonary compromise secondary to tense ascites. Care must be taken with paracentesis to avoid hypotension which will precipitate worsening of intravascular volume depletion and multiorgan dysfunction. Therefore, volume controlled drainage at an initial rate not to exceed 5 mL/kg/hour is advised.

Similarly, thoracentesis is advised for patients with SOS and pleural effusions in the presence of pulmonary dysfunction (recommended 10 mL/kg in children (with a 1.5 L maximum) within the first hour). Pleural drains can be clamped for 24 hours once the drainage is <3 mL/kg/day and removed if there is no re-accumulation after 24 hours.

Ursodeoxycholic acid may be used as prophylaxis in patients at risk for developing SOS. Other medications that may provide some benefit in the treatment of SOS include high dose methylprednisolone which inhibits proinflammatory cytokine production and N-acetylcysteine which is a precursor to the free radical scavenger and anti-oxidant: glutathione. Both cytokine production and low levels of glutathione have been linked to the development of SOS. Additionally, vitamin K and fresh frozen plasma can be used as supportive measures to help correct concurrent coagulopathy secondary to hepatic dysfunction.

40.5.2 Transplant Associated Thrombotic Microangiopathy (TA-TMA)

Transplant associated thrombotic microangiopathy (TA-TMA) is clinically characterized by *de novo* Coombs negative anemia, thrombocytopenia, elevated lactate dehydrogenase (LDH) levels, proteinuria of ≥30 mg/dL, hypertension, and the presence of schistocytes on peripheral smear. It is a potentially fatal complication with a high rate of long-term morbidity and mortality.

Although the pathogenesis is unclear, it involves the dysregulation of either the classical or alternate complement pathways. This leads to endothelial damage that results in small vessel thrombosis and tissue injury. It most frequently affects the kidneys, but can also result in pulmonary hypertension, polyserositis, ischemic bowel changes, PRES, and multiorgan dysfunction syndrome. Risk factors for TA-TMA include high dose chemotherapy and conditioning

regimens that include etoposide, melphalan and platinum-based drugs, busulfan, fludarabine, total body irradiation, infections (most commonly *Aspergillus*, cytomegalo-, adeno-, and BK virus), calcineurin inhibitors, and/or acute GVHD.

The initial treatment of TA-TMA is supportive and includes the management of hypertension, drainage of pleural, pericardial or ascitic fluid, and the treatment of any concurrent infections and acute GVHD. The use of calcineurin inhibitors should be limited, taking care to balance the risk of worsening GVHD. If indicated, alternative GVHD prophylaxis should be initiated. Second-line therapies for TA-TMA include rituximab and therapeutic plasma exchange, but response is often variable. In cases that progress despite supportive measures and have severe multiorgan failure or significant microangiopathic hemolysis, eculizumab, a C5 monoclonal antibody inhibitor provides targeted therapy. Treatment should be continued until symptoms resolve and then continued for approximately 8 weeks as maintenance therapy. Further multicenter study of the role of eculizumab in the treatment of TA-TMA is ongoing.

40.6 Infectious Complications Post-HCT

Infections are a common complication in HCT patients and are associated with high morbidity and mortality.

Given the disruptions to the immune system caused by HCT, it is not surprising that infectious complications are common in HCT recipients. Infections are one of the most common reasons for transfer to the PICU, with a multicenter analysis demonstrating that 46% of HCT patients transferred to PICU have at least one infection. The most common types of infections causing transfer to the PICU are sepsis (including severe sepsis and septic shock) and respiratory infections. In a variety of studies, 12–25% of patients transferred to the PICU were transferred due to sepsis, severe sepsis, or septic shock. Moreover, infection is one of the most frequent causes of death for HCT patients. A study using the VPS (Virtual Pediatric Systems) database demonstrated a mortality rate of 22% in HCT patients with at least one infection. Additionally, the Sepsis Prevalence and Outcomes (SPROUT) study reported a mortality rate of 68% in HCT patients with severe sepsis; the mortality of HCT patients was four-fold higher than non-HCT patients and three-fold higher than other immunocompromised patients without a history of HCT.

When evaluating a potential infection in an HCT recipient, it is important to understand where that patient is in the HCT process, as deficits in both immune defense mechanisms and physical barriers (such as mucosa) evolve over time after HCT. ◘ Figure 40.1 provides an overview of the effects of HCT on the immune system and susceptibility to pathogens. In the initial post-HCT, preengraftment period, the patient has profound neutropenia as well as injuries to mucosal barriers. As a result, the HCT patient at this point is particularly vulnerable to bacterial and fungal infections, which are often derived from the patient's own skin and gastrointestinal (GI) tract microbiota. Among viral infections, herpes simplex virus (HSV) reactivation is common and may contribute to worsening of mucositis. Once engraftment has occurred, adequate neutrophil counts and mucosal healing help control bacterial and fungal infections. However, adaptive immune function, particularly that of T-cells, remains poor and patients are subject to increased risk of viral and fungal infection. After approximately 100 days post-HCT, immune cell populations continue to recover and regain function. At this point, high-risk infections include encapsulated bacteria (particularly in chronic GVHD), varicella-zoster virus (VZV), and fungal infections including *Aspergillus* and *Pneumocystis jiroveci*.

Other factors affecting susceptibility to infections in HCT patients include the type of conditioning regimen, the source of transplanted cells, the underly-

ing disease, and the presence of acute and/or chronic GVHD. For example, nonmyeloablative conditioning may result in less severe and less prolonged neutropenia, although still causing deficits in adaptive immunity, particularly T-cell function. The use of T-cell depleted grafts tends to increase susceptibility to viral and fungal infections. The increased use of antimicrobial prophylaxis in HCT patients has helped to reduce the incidence of infection and related mortality. Specific details of screening and prophylaxis for post-HCT infections may vary somewhat between transplant centers based on local pathogen prevalence and antimicrobial resistance; it is important to understand local practices.

Immunosuppression after HCT may decrease or erase the typical signs and symptoms of infection.

Given the disruption to the immune system after HCT, these children may not present with the typical inflammation-related signs and symptoms, so a high degree of suspicion is important in evaluating these patients. Neutropenic patients will obviously not mount an increased white blood cell count, but may also be impaired in developing other signs related to neutrophil migration such as purulence at a wound site or an infiltrate on chest x-ray. High dose steroids might inhibit the ability to mount a fever.

40.6.1 Bacterial Infections

Bacterial infections are mostly derived from the patient's own flora preengraftment. After >100 days, encapsulated bacteria are more common causes of infection.

Bacterial infections are particularly common in the preengraftment phase (◘ Fig. 40.1). The most common organisms include gram-positive bacteria from the skin or GI tract (coagulase-negative *Staphylococcus*, *Staphylococcus aureus, and Streptococcus* spp.) or gram-negative bacteria from the GI tract (*Escherichia coli*, *Enterobacter* spp., *Klebsiella* spp., and *Pseudomonas* spp.). These infections arise from translocation through compromised physical barriers (i.e., mucosal injury from mucositis and indwelling central venous catheters providing a portal of entry in the skin). Bacterial cultures are the gold standard for diagnosis, but are often negative in these patients given the frequency of pretreatment with antibiotics. Empiric antibiotic coverage will vary depending on local pathogens and antimicrobial resistance profiles, but should provide good gram-positive and gram-negative coverage including activity against pseudomonas. International guidelines have recommended adult HCT patients receive prophylaxis with a fluoroquinolone starting at transplant if they are anticipated to have 7 days or more of neutropenia. Some pediatric transplant centers are extending these recommendations to adolescents.

Overall bacterial infections become less common postengraftment, but there is an increased risk of infection with encapsulated bacteria (particularly *Streptococcus pneumoniae*) after 100 days post-HCT, particularly in patients with chronic GVHD which is associated with splenic dysfunction. Antibiotic prophylaxis for *Streptococcus pneumoniae* is recommended for adults and children with chronic GVHD along with pneumococcal immunizations. Patients with hypogammaglobulinemia (serum IgG level < 400 mg/dL) may be indicated to receive intravenous immunoglobulin (IVIG) in the setting of bacterial infection or as prophylaxis. However, routine IVIG administration for bacterial infection is not recommended.

40.6.2 Fungal Infections

Candida and *Aspergillus* are the most common causes of invasive fungal disease in HCT patients.

Invasive fungal infections are associated with substantial mortality in HCT patients. The most common invasive fungal infections are caused by *Candida* and *Aspergillus* species, generally in the first 100 days post-HCT.

The diagnosis of fungal infections can be challenging given the slow growth on cultures and infections in difficult to sample areas such as the lungs. Histological studies of tissue from infected areas may be required for diagnosis. Useful diagnostic adjuncts for fungal infections include testing for fungal cell wall components, including β-D-glucan (Fungitell®), which is found in all fungi except *Cryptococcus* spp., *Zygomycetes* (including *Mucor* and *Rhizopus*), and *Blastomyces dermatidis*. In addition, *Aspergillus* galactomannan can be measured in serum. Current recommendations are to provide prophylaxis for fungal infections for allogeneic and autologous HCT patients expected to have prolonged neutropenia and/or mucosal damage from the start of conditioning at least until engraftment is achieved. In some patients, lymphocyte recovery, especially in the setting of prolonged immunosuppression as a treatment for GVHD, may be delayed for months or years; these patients may require antifungal prophylaxis postengraftment. The recommended prophylaxis regimen may vary by center depending on local epidemiology of fungal infections and patterns of resistance to antifungal drugs. For patients with prolonged neutropenia or requiring GVHD treatment, who are at higher risk for infection from molds such as *Aspergillus* or fluconazole-resistant *Candida* spp., recommended prophylactic agents include micafungin, posaconazole, or voriconazole. Posaconazole and voriconazole require monitoring of drug levels to avoid toxicity and to assure adequate levels for prophylaxis or treatment of the infection.

Candida infections are the most common cause of invasive fungal disease in the preengraftment period, and can be widely disseminated through the body. Mortality due to invasive Candida infections has been reported to be 10–25%, with higher rates in patients requiring PICU care. Antifungal susceptibilities should be tested on cultured specimens to help guide antifungal treatment. Current consensus recommendations from the European Council on Infections in Leukemia (ECIL-6) are to use one of the echinocandins (caspofungin, micafungin, or anidulafungin) as the first-line therapy. Second-line agents include amphotericin B, fluconazole, and voriconazole. It is important to note that candidemia requires removal of central venous catheters for clearance of infection. In addition, Candida can cause chorioretinitis so ophthalmological evaluation is indicated in invasive Candida infection. Risk factors for invasive Candida infection include previous Candida infection, ongoing immunosuppression (i.e., for GVHD), and receipt of T-cell depleted grafts.

Aspergillus is another common cause of invasive fungal disease associated with mortality rates reported to be as high as 80%. This fungus most commonly causes lung infection, and also has a tendency to cause central nervous system (CNS) disease (about 30% of cases). Of note, it is not susceptible to fluconazole. The first line of recommended anti-fungal agents includes voriconazole, isovuconazole, amphotericin B, or caspofungin. *Aspergillus* is noted for its tendency to be angio-invasive, which can result in devastating hemorrhage particularly in the lungs or the brain. As with candida, fungemia with *Aspergillus* requires removal of central venous catheters for clearance of infection. Risk factors for *Aspergillus* infection are similar to those associated with Candida infection.

Infections with the Zygomycetes (*Rhizopus* and *Mucor*) are less common (less than 35% of fungal infections), but are associated with grim outcomes and 80–90% mortality. These infections particularly favor the sinonasal tract with a propensity to spread locally into the brain. Treatment requires aggressive and early debridement of necrotic tissue and treatment with amphotericin B and/or posaconazole.

Pneumocystis infections generally occur more than 100 days post-HCT. Most HCT recipients receive prophylaxis.

Pneumocystis jiroveci (PJP) is an organism classified as a fungus although previously described as a protozoan. *P. jiroveci* infections typically occur later in the transplant course, greater than 100 days post-HCT, and manifest primarily in the lungs. Prophylaxis is recommended for at least 6 months starting at engraftment for allogeneic HCT recipients as well as autologous HCT patients with underlying malignant disease or who received intensive conditioning regimens. PJP prophylaxis may be extended beyond 6 months for patients who are receiving ongoing immunosuppressive therapy or who have chronic GVHD. The first choice for prophylaxis is trimethoprim-sulfamethoxazole (TMP-SMX) which is not given prior to engraftment due to its myelosuppressive effects. Other options include pentamidine, dapsone, or atovaquone.

40.6.3 Viral Infections

Viral infections after HCT are either reactivation of latent infection or de novo infections. HCT patients with latent infection commonly receive prophylaxis against reactivation.

Viral infections in HCT are frequently caused by reactivation of previously acquired infections, particularly by the herpesviruses (cytomegalovirus, herpes-simplex virus (HSV), Epstein-Barr virus, varicella-zoster virus, etc.), which may also be transmitted in donor cells. HSV tends to reactivate in the preengraftment phase, but other viruses tend to cause infections postengraftment during a period of persistent dysfunction in adaptive immunity. Transplant patients are also vulnerable to new infections including respiratory viruses circulating in the community.

Cytomegalovirus (CMV) is a common latent viral infection that causes active infection in 16–28% of HCT recipients. CMV pneumonia is the most common type of disease, although CMV can affect all organ systems. All HCT recipients should be screened for CMV IgG, and all seropositive patients, or patients receiving a transplant from seropositive donors, will require some degree of antiviral prophylaxis and/or treatment. All allogeneic transplant recipients receive prophylaxis from the time of engraftment to Day 100 and continuing after that if there is a history of CMV disease or the patient is receiving steroids for GVHD. HCT recipients also require ongoing screening, typically on a weekly basis, for evidence of active disease with serum CMV polymerase chain reaction (PCR) assessment or other measurement of viral replication. Any evidence of active CMV infection requires treatment. The first line of therapy is ganciclovir, although it is myelosuppressive and might not be tolerated preengraftment. Other therapeutic options include foscarnet, cidofovir., IVIG, or CMV-specific IgG (Cytogam®).

The herpesviruses CMV, HSV, and VZV are common latent infections that can reactivate post-HCT. Antiviral drugs such as ganciclovir or acyclovir can provide prophylaxis and treatment.

As described above, reactivation with HSV commonly occurs in the preengraftment phase. The most common presentation is the development of mucocutaneous lesions, but disease can be disseminated throughout the body. All HCT recipients should be tested for HSV IgG and seropositive recipients should receive prophylaxis starting at the beginning of conditioning therapy and continuing until engraftment and/or resolution of mucositis. Patients with a history of recurrent HSV reactivations may continue the prophylaxis longer. Acyclovir is the first-line therapy. Ganciclovir will provide sufficient HSV coverage for those patients receiving ganciclovir prophylaxis/treatment for CMV. Oral valacyclovir may be used for patients tolerating oral medications.

Varicella-zoster virus (VZV) reactivation generally occurs later (>100 days) following HCT. Current recommendations are to provide prophylaxis to seropositive HCT recipients with acyclovir or valacyclovir for 1 year after transplant. Any HCT recipient less than 2 years post-transplant who is exposed to a patient with either varicella or zoster infection, or a person who received the VZV vaccine and developed a rash, requires prophylaxis with VZV-specific immunoglobulin (VZIG), or treatment with acyclovir or valacyclovir if VZIG is not available.

Among the other herpesviruses, Epstein-Barr virus (EBV) is most notable in HCT patients for its association with post-transplant lymphoproliferative disorder (PTLD). Antiviral prophylaxis is not currently recommended. Increased viremia with EBV can be treated with reduced immunosuppression or rituximab to avoid PTLD development. Human herpesvirus 6 (HHV-6) has been associated with limbic encephalitis as well as hepatitis, rash, and the idiopathic pneumonia syndrome. Ganciclovir, cidofovir, and foscarnet have *in vitro* activity against HHV-6 and have been reported to be used for treatment.

Adenovirus infection in HCT recipients can represent reactivation or *de novo* infection and can be associated with high mortality rates. Cidofovir and brincidofovir are first-line treatments.

Adenovirus is a common pathogen in pediatric allogeneic HCT recipients, with evidence of viremia in 6–42% of children with allogeneic HCT (versus 3–15% in adults). Adenovirus infection can represent a reactivation or a *de novo* infection. Adenovirus can cause a wide range of diseases, including upper and lower respiratory tract infections, hemorrhagic cystitis, enteritis, myocarditis, hepatitis, nephritis, and disseminated disease involving multiorgan failure. Mortality rates are reported to be as high as 60–80% with disseminated disease. HCT recipients at the highest risk of adenoviral infection are those who received T-cell depleted, haploidentical, or umbilical cord grafts; who have GVHD of grade 2 or higher; or were treated with anti-T-cell antibodies. Weekly viral PCR screening is recommended for these patients. Cidofovir has the most evidence for effectiveness against adenovirus, but it is associated with dose-limiting nephrotoxicity. The more recently developed brincidofovir has demonstrated effectiveness with less nephrotoxicity; however, this is an oral drug and may not be absorbed or tolerated with GI tract pathology. Immune suppression may also be tapered in the presence of significant adenoviral disease.

Respiratory viral infections are common in the community, often following a seasonal pattern, and can result in significant morbidity and mortality in HCT patients. These infections are typically diagnosed by antigen- or PCR-based assays on samples from the respiratory tract (usually nasopharyngeal). Influenza has been associated with increased mortality in HCT patients, and is treated with neuraminidase inhibitors such as oseltamivir or zanamivir depending on local resistance patterns. In addition to isolation protocols in health care settings, patients less than 6 months post-HCT may receive prophylaxis with neuraminidase inhibitors during local influenza season. Inactivated influenza virus vaccination is recommended for parents and other family members and for HCT recipients more than 4 months post-HCT. Another common seasonal pediatric respiratory virus, respiratory syncytial virus (RSV), has been historically reported to be associated with increased morbidity and mortality in HCT patients. More recent studies in pediatric HCT patients have found a low burden of RSV infection among these patients and with minimal mortality, perhaps reflecting the effectiveness of cohorting and isolation of infected patients. Severe RSV disease has been treated with ribavirin, and in some cases, prophylaxis with palivizumab may be appropriate. Other respiratory viruses such as rhinovirus, human metapneumovirus, and parainfluenza virus are also reported with lower frequencies in HCT patients, but can be associated with progression to lower respiratory tract disease and mortality. Ribavirin has been reported as a treatment for human metapneumovirus and parainfluenza virus.

The human polyomaviruses (BK virus and JC virus) are latent viruses that can develop into active infection in the setting of immunosuppression. BK virus is most well known for its association with hemorrhagic cystitis, which is reported to occur in 5–15% of HCT patients, typically at 3–6 weeks post-transplant. Hemorrhagic cystitis can also be associated with adenovirus or CMV infection, or with urotoxic conditioning regimens. Brincidofovir, cidofovir, leflunomide, and fluoroquinolones have been used for the treatment of BK virus hemorrhagic cystitis. JC virus has been associated with late CNS disease, usually progressive multifocal leukoencephalopathy.

New modalities in treating viral infection include multivirus-specific banked T-cells.

Antiviral drugs are often limited by various toxicities. A new modality of treatment for viral infections uses banked, partially HLA matched T-cells that target specific viruses. Single-culture, virus-specific T-cells have been developed that target up to five viruses simultaneously (EBV, adenovirus, CMV, BK virus, and HHV-6). These new treatments may significantly change the treatment of viral infections in HCT patients.

40.6.4 Protozoal Infections

HCT patients may be vulnerable to protozoal infections depending on regional, occupational, or travel exposures. Thus, careful attention to travel history and occupational or recreational exposures is important. Toxoplasmosis is relatively rare in the United States, but more common in parts of Europe. In regions of high prevalence, screening for toxoplasma sero-reactivity may be indicated. HCT patients typically have reactivations of toxoplasma, particularly chorioretinitis or cerebral abscesses. Prophylaxis with TMP-SMX for PCP also provides good coverage for toxoplasma. Other parasitic diseases that may be found depending on the region served are *Strongyloides*, *Plasmodium*, or *Cryptosporidum*.

40.7 Engraftment Syndrome

Engraftment syndrome is characterized by noninfectious fever, systemic vascular leak, dyspnea, hypoxia, pulmonary infiltrates, organ dysfunction, skin rash, and diarrhea. It typically occurs within 4 days of granulocyte recovery.

Engraftment syndrome (ES) is characterized by a constellation of signs and symptoms that include noninfectious fever, systemic vascular leak (hypotension, edema, pleural effusion, ascites, and weight gain), dyspnea, hypoxia, pulmonary infiltrates, organ dysfunction, skin rash, and diarrhea. There is no set universal criteria for the diagnosis of ES, and as a result, its reported incidence varies widely from 17% to 48%. Regardless of the criteria used to diagnose ES, care must be taken to distinguish ES from other post-transplant complications such as acute GVHD, SOS, or sepsis due to their overlapping clinical similarities.

The pathophysiology of ES is hypothesized to be the result of a proinflammatory state due to an increase in leukocyte activation and proinflammatory cytokines as a result of endothelial cell damage that occurs in the pretransplant conditioning regimen. While ES occurs on average 10–28 days post-HCT, it typically occurs within 4 days of granulocyte recovery. Preengraftment syndrome (PES) is a similar condition that can occur after umbilical cord transplant as early as 3–7 days post-transplant (◘ Table 40.8).

Risk factors for ES include HLA mismatched transplants, patients less than 8 years of age, the number of infused CD34+ cells, and total body irradiation. Engraftment syndrome can self-resolve in 30% of cases without treatment; however, if it persists, it may lead to increased nonrelapse mortality. Treatment is indicated in the presence of persistent noninfectious fever or severe manifestations of capillary leak such as pulmonary edema. Management involves supportive care with antipyretics, oxygen supplementation, diuretics, and if needed, systemic corticosteroids using methylprednisolone (1 mg/kg/day). ES is typically very corticosteroid responsive and symptoms usually resolve in less than 7 days.

40.8 Graft Versus Host Disease

Graft versus host disease (GVHD) is a potentially debilitating complication of allogenic HCT that occurs due to a dysregulated immune response by activated donor T-cells (and sometimes B-cells) against host cells resulting in inflammation and apoptosis. Historically divided into acute GVHD, occurring within

Table 40.8 Comparison of differential diagnoses of engraftment syndrome

	Clinical features	Onset of symptoms
Engraftment syndrome	Noninfectious fever Signs of vascular leak Weight gain Organ dysfunction	10–28 days post-HCT (usually within 4 days of neutrophil engraftment)
Preengraftment syndrome	Noninfectious fever Signs of vascular leak Weight gain Organ dysfunction	3–7 days post-HCT
SOS	Weight gain Hepatomegaly Ascites Hyperbilirubinemia Unexplained consumptive and transfusion- refractory thrombocytopenia	Usually within 30 days post-HCT (delayed onset SOS has been reported)
Acute GVHD	Noninfectious fever Signs of vascular leak Rash with histological features of GVHD Hyperbilirubinemia	Commonly within the first 100 days post-HCT
Sepsis	Infectious cause of fever Systemic inflammatory response	Any point in time

SOS sinusoidal obstruction syndrome, *GVHD* graft versus host defense, *HCT* hematopoietic cell transplan

100 days of transplant, and chronic GVHD occurring thereafter, this distinction is no longer based on time. Instead, it is now based on clinical symptoms, with overlap syndrome displaying features of both acute and chronic GVHD.

The incidence and severity of GVHD can vary widely and is dependent on multiple factors. Factors that increase the risk of GVHD include: an older age of the donor, female donors, HLA disparity, the use of peripheral blood stem cells as the donor source, concurrent CMV infection, infusion of donor lymphocytes post-HCT for the treatment of recurrent malignancy, inadequate GVHD prophylaxis, and T-cell replete grafts.

The major target organs of acute GVHD are the skin, liver, and intestinal tract, all of which contain high numbers of antigen presenting cells.

Management of acute GVHD is based on severity (Tables 40.9 and 40.10) and involves prevention, treatment, and symptomatic management. Pretransplant prophylaxis may include *in vivo* T-cell depletion with anti-thymocyte globulin and *ex vivo* donor T-cell depletion. Post-transplant immune modulation is achieved through the use of calcineurin inhibitors (e.g., tacrolimus) with strict drug level monitoring to maintain therapeutic levels and to avoid toxic supra-therapeutic effects. Methotrexate, corticosteroids, and mycophenolate mofetil are also used for prophylaxis.

Management of acute GVHD is based on severity and involves prevention, treatment, and symptomatic management.

The mainstay of treatment for acute GVHD is corticosteroids which are effective in up to 60% of cases. Steroid refractory or unresponsive acute GVHD requires second-line agents with either monoclonal antibodies such as infliximab (tumor necrosis factor-alpha blocker) and basiliximab (IL-2 receptor blocker) or extracorporeal photopheresis (ECP) which causes the functional inactivation of allo-reactive T-cells.

Chronic GVHD is one of the leading causes of late nonrelapse morbidity and mortality after HCT, negatively impacting the quality of life of long-term

Table 40.9 Stages of acute graft versus host disease (GVHD)

Stage	Skin	Liver (bilirubin mg/dL)	Gastrointestinal	
			Lower GI stool/day (mL/kg/day)	Upper GI symptoms
O	No rash	≤2.0	<10	–
I	Maculopapular rash <25% BSA	2.1–3.0	10–19.9	Persistent nausea and vomiting
II	Maculopapular rash 25–50% BSA	3.1–6.0	20–30	Persistent nausea and vomiting
III	>50% generalized erythroderma	6.1–15.0	>30	Persistent nausea and vomiting
IV	Generalized erythroderma with bullae and desquamation	>15.0	Severe abdominal pain with or without ileus; lower GI bleeding	Persistent nausea and vomiting

BSA body surface area, *GI* gastrointestinal

Table 40.10 Grades of acute graft versus host disease (GVHD)

Overall grade	Stage based on organ involvement			First-line treatment
	Skin	Liver	Lower GI	
I	1–2	None	None	Topical corticosteroids
II	3	1	1	Methylprednisolone (2 mg/kg/day) Nonabsorbable steroids can be considered for GI GVHD
III	–	2–3	2–4	Methylprednisolone (2 mg/kg/day) Nonabsorbable steroids can be considered for GI GVHD
IV	4	4	–	Methylprednisolone (2 mg/kg/day)

GI gastrointestinal

survivors and prolonging their need for immunosuppression. It occurs in up to 25% of pediatric patients and its clinical and molecular manifestations are similar to those found in some autoimmune conditions. Clinical features include scleroderma-like skin manifestations, fasciitis leading to contractures and decreased range of motion across joints, bronchiolitis obliterans (BO), bronchiolitis obliterans organizing pneumonia (BOOP), polyserositis, and intestinal fibrosis resulting in malabsorption, hepatic dysfunction, and frequent infections due to lymphoid hypocellularity. Corticosteroids are recommended as the first-line treatment for chronic GVHD, with calcineurin inhibitors and early use of ECP as steroid sparing strategies. Rapamycin (mTOR inhibitor) and pentostatin are recommended for refractory chronic GVHD. Rituximab is suggested as a second-line treatment option in refractory cutaneous or musculoskeletal chronic

GVHD and imatinib is suggested as a second-line treatment option in refractory pulmonary or sclerodermatous chronic GVHD. Stringent infection prophylaxis is essential as infection is the leading cause of death among these patients. Prophylaxis against *Pneumocystis jiroveci* should be administered for at least 6 months after the discontinuation of immunosuppressive medications. Prophylactic acyclovir should be used for the prevention of VZV reactivation during the first year after transplantation, and later if systemic immunosuppression is still needed to control chronic GVHD. Prophylaxis against encapsulated bacterial pathogens and invasive fungal infections are also important. Immune reconstitution testing helps guide clinicians regarding the duration needed for anti-microbial prophylaxis. IVIG can also be given to patients with hypogammaglobulinemia to maintain serum IgG levels above 400 mg/dL.

40.9 Neurologic Complications Post-HCT

Neurological complications are common in HCT patients and are associated with significant morbidity and mortality.

Neurological disorders are cited as the cause for PICU transfer in 10–33% of HCT patients. These complications can be the result of CNS infection, metabolic derangements (due to medication or organ dysfunction), anatomical or metabolic abnormalities associated with the underlying diagnosis, or cerebrovascular events. Neurologic complications account for 10–15% of HCT-related mortality. Presenting symptoms may include seizure, encephalopathy, altered mental status, headache, or focal neurological signs. A history of a neurological event prior to HCT (whether due to the underlying disease or medication toxicity) increases the risk of neurological complications post-HCT.

Posterior reversible encephalopathy syndrome (PRES) is a common complication in the first 100 days post-transplant, characterized by headache, seizures, mental status changes, visual changes, and hypertension.

The posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS), is one of the most common neurological complications in HCT patients, occurring in 6–9% of HCT recipients, and frequently prompting transfer to the PICU. PRES is typically observed in the first 100 days post-transplant. Presenting symptoms are headache, acute mental status changes, visual changes including cortical blindness, and seizures, generally in association with an acute rise in blood pressure.

Magnetic resonance imaging (MRI) is the recommended imaging modality and classically reveals signal abnormalities on FLAIR imaging in the posterior regions of the brain, reflective of vasogenic edema (◘ Fig. 40.2). It is theorized that cerebral vascular dysregulation, in response to elevated blood pressure or to endothelial activation, is responsible for causing vasogenic edema. The edema most commonly occurs in the parieto-occipital regions, but may be found elsewhere. PRES has most commonly been associated with the administration of calcineurin inhibitors (cyclosporine and tacrolimus), but also with sirolimus and dexamethasone.

PRES is treated by stopping or reducing the offending medication (usually calcineurin inhibitors) and controlling seizures and hypertension.

Treatment of PRES includes seizure control with benzodiazepines or other anti-epileptic drugs as well as treatment of hypertension. Intravenous continuous administration of anti-hypertensives such as nicardipine or esmolol allows rapid titration of the effect. If a patient is chronically hypertensive, it is important to not reduce the blood pressure below the normal baseline of the patient due to changes in cerebral autoregulation to adapt to higher blood pressures. As calcineurin inhibitors are the usual culprit in PRES, even at nontoxic serum levels, holding, reducing the dose, or changing to another medication for GVHD prophylaxis is indicated.

As suggested by the name, PRES is usually reversible. However, it has been associated with severe morbidity and mortality including status epilepticus, intracranial hemorrhage, and brain herniation. The potential for these complications must be considered if a patient's status does not improve or deteriorates. In addition, some patients with PRES continue to have seizures in the

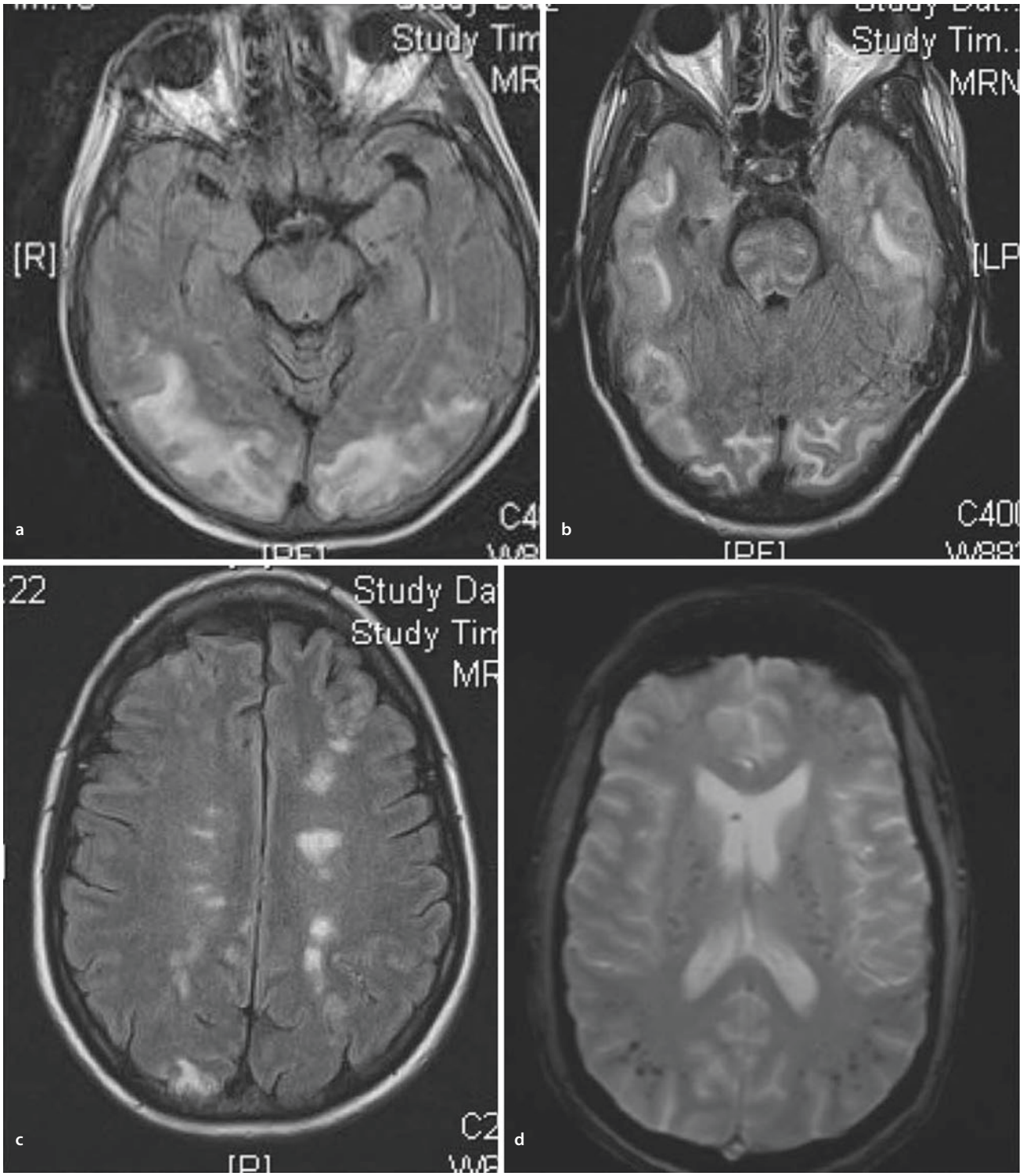

Fig. 40.2 Posterior reversible encephalopathy syndrome (PRES) variants. **a** Classic PRES with bilateral posterior signal abnormality on FLAIR MRI. **b** Bilateral predominantly, but not exclusively posterior signal abnormality on FLAIR MRI reflects vasogenic edema. **c** Multiple areas of FLAIR abnormality in periventricular region on FLAIR MRI in patients with thrombocytopenia on tacrolimus after HCT for AML. **d** Same patient as in **b** with gradient echo MRI (**c**) showing evidence of small hemorrhages in affected areas. *FLAIR* indicates fluid-attenuated inversion recovery, *MRI* magnetic resonance imaging, *HCT* hematopoietic cell transplantation, *AML* acute myeloid leukemia. Pruitt et al. (2013)

short- to long-term. Treatment with anti-epileptic medications may be required beyond the initial presentation with PRES.

CNS infections may have subtle findings in HCT patients, requiring a high index of suspicion.

CNS infections in HCT patients are relatively rare, but are associated with high rates of morbidity and mortality. These patients present with a wide range of symptoms including fever, seizures, headache, encephalopathy, and focal neurological signs. HCT recipients, particularly in the preengraftment period, will have limited ability to mount an inflammatory response which may decrease the severity of symptoms of a CNS infection. In this setting, one should have a low threshold of suspicion for obtaining CNS imaging and sampling cerebrospinal fluid.

The viruses most commonly associated with acute encephalitis are HHV-6, CMV, adenovirus, HSV, and VZV. MRI may be useful. For example, HHV-6 is associated with a pattern of bilateral limbic involvement. Additionally, viruses can be detected in the cerebrospinal fluid by PCR or culture. Fungal CNS disease is most commonly caused by *Aspergillus*, resulting in mass lesions that are at high risk for hemorrhagic conversion given the angio-invasive proclivity of *Aspergillus*. *Candida* is the most common cause of fungal meningitis in HCT patients. Zygomycetes (e.g., *Mucor* and *Rhizopus*) invades the brain from local infection in the sinuses or nasal passages, and is associated with very high mortality rates despite aggressive debridement and antifungal treatment. Bacterial meningitis and cerebral abscesses can be caused by gram-positive and gram-negative bacteria including anaerobes from the patient's own microbial flora. Toxoplasma reactivation can produce cerebral abscesses that might not have the classic ring-enhancing appearance on imaging in the setting of neutropenia. In situations where there is an abscess causing a mass effect, neurosurgical intervention and drainage might be indicated. All acute CNS infections require aggressive and *prolonged* treatment with parenteral antimicrobial agents. Progressive multifocal leukoencephalopathy is a demyelinating disease due to JC virus infection that is found late (months to years) post-HCT; the only treatment is decreasing immunosuppression.

Medications and metabolic derangements can cause seizures, encephalopathy, and other neurological symptoms.

Medications can have neurological effects beyond PRES. Seizures are known to be associated with a number of medications commonly administered to HCT patients in conditioning regimens and/or post-HCT. Chemotherapeutic agents associated with seizures include busulfan, cyclophosphamide, cytarabine, fludarabine, and melphalan. Prophylaxis with anti-epileptic medications is common with busulfan administration. In addition, several anti-infective agents may also be associated with encephalopathy as well as seizures. Radiation and methotrexate can be associated with a more delayed encephalopathy (>100 days post-HCT). Treatment of drug-related neurologic symptoms includes treating seizures and metabolic derangements and discontinuing the offending medication if possible.

Neurological symptoms including seizures and encephalopathy can also be associated with metabolic derangements. These may be secondary to medication effects such as the syndrome of inappropriate antidiuretic hormone (SIADH) associated with cyclophosphamide. Metabolic derangements may also be secondary to organ dysfunction such as uremia in renal failure or hyperammonemia in liver failure.

GVHD primarily causes neurologic problems secondary to treatment with calcineurin inhibitors, resulting in PRES and other disorders. However, chronic GVHD can be associated with immune dysregulation that results in a variety of demyelinating and vasculitic CNS disorders.

Cerebrovascular events are relatively rare, but cause potentially devastating complications of HCT. Intracranial bleeding, whether intraparenchymal, subarachnoid, or subdural, can be associated with thrombocytopenia, coagulopathy (as may occur in liver dysfunction in SOS), and hypertension. Certain

infections can also increase the risk of intracranial bleeding due to invasion of blood vessels by the infectious organism (e.g., *Aspergillus*) or due to vasculitis (e.g., with VZV encephalitis). When intracranial hemorrhage is suspected, CT imaging is the fastest imaging modality to confirm the diagnosis. Patient management includes transfusion of platelets, correction of coagulopathy, and cautious reduction of blood pressure, along with standard supportive care of patients with an intracranial mass and elevated intracranial pressure (ICP). A neurosurgical consult should be obtained and operative intervention may be indicated. Ischemic strokes may also occur, especially in conjunction with infection-associated vasculitis or endothelial injury as it occurs in TA-TMA. Patients undergoing HCT for sickle cell disease are particularly at risk for ischemic stroke. The treatment of an ischemic stroke will vary depending on the severity and underlying cause; with extensive lesions, intensive ICP management and neurosurgical intervention may be needed.

Always consider CNS recurrence of malignant disease in a HCT patient with neurological symptoms.

The underlying disease may also result in specific neurological complications. As mentioned above, sickle cell disease patients undergo HCT with abnormal cerebral blood vessels that predispose to ischemic stroke. Patients with CNS malignancy may be at risk for obstructive hydrocephalus given residual tumor or previous surgery, or may already have a ventriculoperitoneal shunt. Patients with Hurler syndrome also have a high rate of obstructive hydrocephalus and shunt placement. With these patients, shunt malfunction or worsening hydrocephalus should always be considered in the setting of neurological symptoms. Finally, for patients with malignant disease, CNS recurrence or relapse must be a consideration in the differential diagnosis for any neurological changes.

40.10 Post-transplant Lymphoproliferative Disease

The principal treatment for post-transplant lymphoproliferative disease (PTLD) has consisted of cytotoxic chemotherapy using regimens developed for non-Hodgkin lymphoma, and more recently, the B-cell monoclonal antibody rituximab. Additionally, the use of Epstein-Barr virus (EBV) cytotoxic T-lymphocytes has provided promising results for the management of EBV + PTLD.

Post-transplant lymphoproliferative disease (PTLD) is the most common post-HCT malignancy in children. It is commonly associated with EBV infection, although EBV negative disease also occurs. According to the World Health Organization 2008 classification, PTLD can be classified into early lesions, polymorphic PTLD, monomorphic PTLD, and Hodgkin-like PTLD. The course of the disease varies from indolent, localized lymphadenopathy, to rapidly progressive fulminant disease (usually associated with post-HCT PTLD). The degree of immunosuppression appears to be a major determinant for the development of PTLD due to the consequent impairment of EBV-specific T-cell-mediated immunity, which in turn allows EBV-induced B-cell proliferation. While EBV+ PTLD occurring in the setting of solid organ transplantation is sometimes polyclonal and may respond to reduction in immunosuppression, EBV+ PTLD post-HCT is typically monoclonal and rarely responds solely to immunosuppression reduction. In fact, reduction of immunosuppression may be contraindicated following HCT because of the risk of inciting or exacerbating acute or chronic GVHD. The principal treatment for PTLD has consisted of cytotoxic chemotherapy using regimens developed for non-Hodgkin lymphoma, and more recently, the B-cell monoclonal antibody rituximab. EBV+ PTLD is an aggressive malignancy, which in the pre-rituximab era had a median overall survival of 31 days; patients with EBV+ PTLD that have an incomplete response or fail to respond to rituximab have a median overall survival of 33–56 days. Recently, the use of EBV cytotoxic T-lymphocytes has provided promising results for the management of EBV + PTLD. Tumor flare (or pseudo-progression) has been reported in response to this T-cell directed therapy and is an important consideration when tumors are in the proximity of vital structures.

40.11 Chimeric Antigen Receptor (CAR)-Immune Effector Cell Therapy

A chimeric antigen receptor (CAR) is a genetically modified receptor that has three major components, an extracellular antigen recognition domain, a transmembrane domain, and an intracellular signaling domain. The extracellular component allows the recognition of a specific antigen on the target cell (e.g., CD19 in acute lymphoblastic leukemia and non-Hodgkin lymphomas) and the intracellular signaling domain will stimulate cellular proliferation, cytokine release, and elimination of the target cell. Manufacturing the CAR can be performed using viral (e.g., lentivirus or retrovirus vectors transduction) or nonviral (electroporation) gene modification of the immune effector cells (T-lymphocytes or natural killer cells). Tisagenlecleucel is the first chimeric antigen receptor autologous T-cell immunotherapy approved by the Food and Drug Administration (FDA) for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.

This adoptive cellular therapy has been reported to be associated with strikingly high sustainable remission rates, but is also associated with unique toxicities, namely, cytokine release syndrome (CRS) and neurotoxicity (previously known as CAR T-cell Related Encephalopathy Syndrome (CRES); recently referred to as Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)).

40.11.1 Cytokine Release Syndrome (CRS)

Cytokine release syndrome (CRS) is a systemic inflammatory response caused by the activation and expansion of immune effector cells including lymphocytes and/or myeloid cells (B-cells, T-cells, NK-cells, macrophages, and monocytes) and the release of very high levels of cytokines. CRS has been reported with other immunotherapy strategies including monoclonal antibodies such as anti-CD52 (alemtuzumab), T-cell engaging monoclonal antibodies (blinatumomab), and haploidentical hematopoietic cell transplantation. High levels of gamma interferon, tumor necrosis factor-alpha, and interleukin-6 (IL6) are the main cytokines associated with CRS. Further, CRS has been reported in 77% of pediatric and young adult patients who were treated with CD19 CAR T-cells; half of them (47%) required critical care support due to severe CRS (≥ grade III) with a median ICU stay of 7 days (range 1–34). Almost half of the patients (44%) developed hypoxia and required oxygen supplementation, 13% required invasive mechanical ventilation, 25% were treated with high dose vasopressors, and 9% underwent renal replacement therapy. The median time to CRS onset and resolution was 3 days (range 1–22) and 8 days (range 1–36), respectively. Patients with CRS usually present with fever, tachycardia, hypoxia (arterial oxygen saturation < 90% on room air), hypotension and, in severe cases, multiorgan failure (hepatic, renal, cardiac dysfunction, and coagulopathy). Risk factors associated with severe CRS include early onset fever (<3 days post CAR T-cell infusion), large tumor burden, and co-existing morbidities. The clinical presentation of CRS can range from very mild grade I (low grade fever and tachycardia) to very severe grade IV CRS (respiratory failure requiring mechanical ventilation, shock, multiorgan failure, and death). Grade I CRS can be managed with supportive measures only (antipyretics) and anti-IL6 therapy (tocilizumab) can be considered for persistent symptoms. Grade II CRS usually presents with hypotension that responds to intravenous fluid and/or low dose vasopressor treatment, and hypoxia that requires oxygen supple-

mentation <40% FiO_2. Anti-IL6 therapy and corticosteroids should be considered in patients not responding to supportive measures and fluid resuscitation. Grade III CRS is characterized by severe hypotension requiring multiple vasopressors (including vasopressin) and/or severe hypoxia requiring >40% FiO_2 supplementation and/or noninvasive respiratory pressure support. Grade IV CRS is defined as persistent hypotension despite fluid resuscitation and multiple vasopressors, and a requirement for mechanical ventilation. In the pivotal ELIANA trial, 50% of the patients received one dose of tocilizumab, 13% received 2 doses, and 6% received 3 doses. One fourth (26%) of the patients required the addition of corticosteroids. The use of anti-IL6 therapy and steroids for patients with CRS did not appear to affect CAR T-cell therapy outcomes. As new immune effector cells are introduced, some have an added "safety switch" designed to eliminate transduced cells, such as anti-CD19 CAR T-cells also expressing inactive, truncated EGFR, which enables the cells to be targeted through administration of the anti-EGFR antibody cetuximab. A natural killer cell product under study has included a "suicide" gene – inducible caspase-9 – that may be pharmacologically activated to eliminate the transduced cells. Functional co-expression of RQR8, a construct combining epitopes from CD34 and CD20, renders CAR T-cells sensitive to the monoclonal anti-CD20 antibody rituximab. Immune effector cell therapies are rapidly emerging. Prompt recognition and management of CRS are essential to optimize outcomes. Specific management decisions are best made in collaboration with immune effector cell clinical teams and should be based on institutional procedures, protocol-specific guidelines, and/or product label specifications.

40.11.2 CAR T-Cell Related Encephalopathy Syndrome (CRES) or Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)

Neurologic toxicities associated with CAR T-cell therapy may include confusion, encephalopathy, tremor, delirium, agitation, somnolence, seizures (convulsive or nonconvulsive), cerebral edema, coma, and death. These may occur simultaneously with CRS, following resolution of CRS or with no antecedent CRS. Grade I CRES usually presents with mild confusion, headache, or tremor. Grade II can be associated with a brief seizure, while grade III is associated with multiple generalized seizures. Grade IV presents as obtundation, deep coma requiring airway protection, and mechanical ventilation. Maude reported neurologic events in 40% of pediatric patients with acute lymphoblastic leukemia who received tisagenlecleucel within 8 weeks post CAR T-cell infusion; 13% developed grade III and none experienced grade IV. Neurotoxicity was more frequent in patients with higher grade CRS. In half of the patients, the neurotoxicity resolved within 10 days and 75% resolved within 18 days of onset. Detailed neurologic assessment tools include the CARTOX-10 point neurologic assessment scoring for patients ≥12 years and the Cornell Assessment of Pediatric Delirium (CAPD) for patients <12 years and/or based on the developmental level. Grade IV neurotoxicity can present as cerebral edema and death. It is recommended that patients with CNS disease and/or a history of seizure disorders receive antiseizure prophylaxis starting at least as early as the day of infusion and continuing for at least 30 days post CAR T-cell therapy. Patients with severe CAR T-cell related neurotoxicity require prompt transfer to the intensive care unit, and neurology consultation and CNS imaging should be strongly considered. It is important that thrombocytopenia and coagulopathy be corrected/avoided to reduce the risk of catastrophic cerebral hemorrhages. In general, steroids are first-line

agents for CRES/ICANS and anti-IL6 therapy may be used concomitantly among patients with concurrent CRS. As with CRS, specific management decisions are best made in collaboration with immune effector cell clinical teams and should be based on institutional procedures, protocol-specific guidelines, and/or product label specifications.

40.12 Summary

Children undergoing HCT represent a high-risk group of patients who frequently require critical care services for a wide variety of infectious and noninfectious pathologic conditions. A sound understanding of the HCT process, its unique and common complications and the potential treatment of these conditions will afford the pediatric critical care provider the best opportunity to intervene effectively and improve outcomes for this most vulnerable patient population. A collegial and collaborative approach by the many disciplines involved in the care of these children would appear essential in optimizing their outcomes. Although outcomes appear to have improved over time, much work remains to impact the substantial morbidity and mortality incurred by children undergoing HCT.

Review Questions

1. A 12 month old male who is Day +7 from a HCT for Hurler disease is transferred to the PICU for fever and hypotension that has persisted despite three boluses of 20 mL/kg normal saline and the initiation of a dopamine infusion at 5 mcg/kg/min. On physical exam, the patient is irritable with severe mucositis, cool extremities with 4 second capillary refill, and coarse breath sounds bilaterally. The heart rate is 150 beats per minute, the blood pressure is 70/40 mmHg, the respiratory rate is 40 breaths per minute, and his oxygen saturation on pulse oximetry is 92% while receiving 40% oxygen via aerosolized face mask. Which of the following is the most likely organism to be the source of the septic shock in this patient?
   A. Aspergillus
   B. Herpes Simplex Virus
   C. *Pseudomonas aeruginosa*
   D. *Streptococcus viridans*

2. A rapid response team is called for a 12 year old girl on the HCT unit with generalized tonic-clonic seizure activity. She is Day +46 from an allogeneic HCT for relapsed acute lymphoblastic leukemia. Her mother reports that the patient had been complaining of a headache and blurry vision for a couple of hours prior to the onset of the seizures. She has been diagnosed with acute GVHD. Medications include fluconazole, ganciclovir, cefepime, and tacrolimus. Vital signs reveal the following: temperature – 37.2°, heart rate – 110 beats per minute, blood pressure – 150/100 mmHg, respiratory rate – 20 breaths per minute. The patient is transferred to the PICU. Which of the following would NOT be an indicated treatment for this patient?
   A. Increase tacrolimus dose to treat GVHD
   B. Lorazepam (0.1 mg/kg) for seizure treatment
   C. Obtain stat head CT scan to rule out intracranial bleeding
   D. Start a nicardipine infusion for controlled reduction in blood pressure to 130/80 mmHg

3. A 14 year old male with acute myelocytic leukemia, Day +17 s/p allogeneic HCT is being transferred to the PICU for the acute onset of respiratory distress. His vital signs reveal a temperature of 39.2°, heart rate – 125 beats per minute, blood pressure – 145/92 mmHg, and respiratory rate – 38 breaths per minute. His oxygen saturation is 93% on pulse oximetry while receiving 60% oxygen via face mask. On clinical exam, he is dyspneic with intercostal retractions and diffuse rales heard on auscultatory exam. He has a cough, but no evidence of hemoptysis. His peripheral pulses are strong and his capillary refill is 2 seconds. His laboratory analysis reveals an absolute neutrophil count >500 cells/μL for the second day in row. His chest radiograph reveals bilateral parenchymal opacifications. Results of bronchoscopic alveolar lavage performed earlier in the day revealed no evidence of infection and 35% hemosiderin laden macrophages. Which of the following best describes his pulmonary condition?
   A. Engraftment syndrome is the most likely cause of his respiratory distress, but he has not satisfied pediatric acute respiratory distress syndrome criteria.
   B. He has diffuse alveolar hemorrhage as the cause of his respiratory distress, but he has not satisfied pediatric acute respiratory distress syndrome criteria.
   C. He has pediatric acute respiratory distress syndrome secondary to diffuse alveolar hemorrhage.
   D. He has pediatric acute respiratory distress syndrome secondary to engraftment syndrome.

4. A 12 year old, 33 kg female with acute myelocytic leukemia, Day +24 s/p allogeneic HCT is admitted to the PICU with the acute onset of respiratory distress and abdominal distention. On clinical exam, she is tachypneic and with end expiratory grunting, She is tachycardic with a regular rhythm and adequate peripheral pulses. Her abdomen is markedly distended with hepatomegaly and right upper quadrant tenderness. She has generalized edema and her weight is up 3 kg since she received her stem cell transplant. On laboratory analysis, her bilirubin has steadily increased and is now 3.7 mg/dL; her prothrombin time is 22.5 seconds with an international normalized ratio (INR) of 2.2. A doppler hepatic ultrasound demonstrated reversal of blood flow in the hepatic veins and a hepatic artery resistance index of 0.95. Which of the following medications is most likely to be of benefit in treating her acute condition?
   A. Defibrotide
   B. N-acetylcysteine
   C. Solumedrol
   D. Ursodeoxycholic acid

5. A 7 year old male, Day +67 s/p allogeneic HCT for refractory leukemia has developed multiple organ dysfunction syndrome characterized by acute renal failure and echocardiographic evidence of pulmonary hypertension. He is being treated with tacrolimus for acute graft versus host disease. His blood chemistries are notable for a blood urea nitrogen (BUN) concentration of 73 mg/dL, a creatinine of 2.1 mg/dL and a lactate dehydrogenase level of 1749 mg/dL. His complete blood count reveals a Coombs negative anemia, a new and progressive thrombocytopenia, and schistocytes on the peripheral smear. His coagulation profile is unremarkable. A tentative diagnosis of transplant associated thrombotic microangiopathy is made. All of the following should be considered in the treatment of this condition EXCEPT:

A. Assurance of appropriate antimicrobial therapies
B. Discontinuation of the tacrolimus and transition to other acute GVHD therapies
C. Initiation of complement blocking antibodies such as eculizumab
D. Initiation of corticosteroid therapy

6. Cytokine release syndrome (CRS) has been associated with a recently approved pre B-cell directed CAR T-cell therapy. Which of the following agents is used in the management of mild to moderate CRS?
A. Anti-C5 antibody (eculizumab)
B. Anti-CD19 antibody (blinatumomab)
C. Anti-CD20 antibody (rituximab)
D. Anti-IL6 antibody (tocilizumab)

7. Which of the following is NOT a characteristic feature of engraftment syndrome in a child receiving a matched unrelated hematopoietic cell transplant?
A. Absolute neutrophil count >500 cells/μL
B. Fever
C. Post-transplant Day +2
D. Pulmonary edema

8. Which of the following is a late pulmonary complication after hematopoietic cell transplant?
A. Bronchiolitis obliterans syndrome
B. Diffuse alveolar hemorrhage
C. Idiopathic pneumonia syndrome
D. Transplant associated thrombotic microangiopathy

9. A 5 year old child with pre B-cell ALL with match sibling hematopoietic cell transplant Day +30 presents with fever, worsening body edema, pallor and dark colored urine. On laboratory assessment, his creatinine level is 2.1 mg/dL and his platelet count is 37,000/μL. Which of following is the most likely cause for these clinical features?
A. Acute graft versus host disease
B. Idiopathic pneumonia syndrome
C. Sinusoidal obstruction syndrome
D. Transplant associated thrombotic microangiopathy

Answers

1. D
2. A
3. C
4. A
5. D
6. D
7. C
8. A
9. D

Suggested Readings

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Transfusion Medicine

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Contents

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Learning Objectives

After completing this chapter, the reader should have an understanding of:

- The indications for the transfusion of red blood cell and plasma/coagulant blood products
- The current data regarding red blood cell transfusions in critically ill children
- The indications for irradiated, filtered, and/or leukoreduced blood products
- The types of transfusion reactions and their treatment
- The risks associated with blood product transfusions
- The complexities of transfusion therapy in special patient populations.

41.1 Introduction

Blood product transfusions are commonly utilized in critically ill children managed in the pediatric intensive care unit (PICU), pediatric cardiac intensive care unit (PCICU), and pediatric cancer/transplant centers and can be lifesaving. However, there is a growing body of literature that demonstrates while these therapies are often beneficial, they are associated with significant risks and adverse outcomes, even after controlling for illness severity. Furthermore, examination of hospital transfusion practices has demonstrated a 134% increase in transfusions from 1997 to 2011 and that 50% of these transfusions are "unnecessary" (Joint Commission 2017). In response, medical centers have embraced patient blood management, an evidence-based, multidisciplinary patient safety initiative focused on blood conservation, control of bleeding, anemia management, and safe and restrictive transfusion practices. It is in this climate that the pediatric intensivist must have a thorough understanding of blood product components and their indications, the associated risks, and the transfusion needs of particular patient populations (Table 41.1 and 41.2).

41.2 Red Blood Cell Transfusions

Critically ill children often present with chronic anemia from ongoing inflammatory processes and nutritional deficits. This anemia can be exacerbated by iatrogenic factors associated with critical care such as frequent blood sampling for laboratory tests, hemodilution from large volume resuscitation, and blood loss during procedures and/or surgery. Acute anemia results following trauma and surgery and in settings of sepsis/acute inflammation and bone marrow suppression, or pathologic hematologic-oncologic processes. In one large multicenter pediatric study, 33% of patients were anemic on admission to the PICU and another 41% developed anemia during the admission. The management of anemia depends on its etiology, severity, and rate of occurrence, as well as the pathophysiologic state of the child and the risk for ongoing end organ injury.

41.2.1 Physiology

The two most common indications given for red blood cell (RBC) transfusion are a measured low hemoglobin (Hb) concentration and to improve oxygen delivery by increasing arterial oxygen content. It is understood that anemia decreases the oxygen-carrying capacity of the blood, and thereby oxygen delivery to the tissues. Following this logic, augmentation of tissue oxygen delivery

Table 41.1 Blood components and plasma derivatives

Component/ product	Composition	Approximate volume	Indication
Whole blood	RBCs, plasma, WBCs, platelets	500 mL	Increase RBC mass and plasma volume (WBCs/ platelets not functional)
			Deficient in Factor V and Factor VIII
Red blood cells	RBCs, WBCs, platelets	250–350 mL	Increase RBC mass in symptomatic anemia (WBCs/platelets not functional)
RBC leukocyte-reduced (filtered)	85% original volume of RBCs, $<5 \times 10^6$ WBC, few platelets, minimal plasma	250–350 mL	Increase RBC mass; $<5 \times 10^6$ WBC
			Decreased febrile reactions, alloimmunization to WBC (HLA antigens), or CMV transmission
RBCs washed	RBCs, $<5 \times 10^6$ WBC, no plasma	180 mL	Increase RBC mass; reduced risk of allergic reactions to plasma proteins
Granulocytes	Granulocytes ($>1.0 \times 10^{10}$ PMN/unit Lymphocytes, Platelets ($>2.0 \times 10^{11}$/ unit), some RBCs (<500 PMN/μL)	220 mL	Provide granulocytes for selected patients with sepsis and neutropenia
Platelets	Platelets ($>5.5 \times 10^{10}$/ unit), RBCs, WBCs, plasma	50 mL	Bleeding due to thrombocytopenia or thrombocytopathy
Platelets pheresis	Platelets ($>3.0 \times 10^{11}$/ unit), RBCs, WBCs, plasma	300 mL	Same as platelets; sometimes HLA matched
Platelets leukocyte-reduced	Platelets ($>3.0 \times 10^{11}$/ unit), $<5 \times 10^6$ WBC per final dose of pooled platelets	300 mL	Same as platelets; $<5 \times 10^6$ WBC to limit febrile reactions to leukocytes (HLA antigens) or CMV transmission
FFP	FFP, Donor retested plasma has all coagulation factors, Thawed plasma has reduced Factor V and Factor VIII	220 mL	Treatment of some coagulation disorders

(continued)

Table 41.1 (continued)

Component/ product	Composition	Approximate volume	Indication
Cryoprecipitate	Fibrinogen, Factor VIII, Factor XIII, von Willebrand factor	15 mL	Deficiency of fibrinogen or Factor XIII; second choice for treatment of hemophilia A, von Willebrand disease
Human factor VIII	Factor VIII plasma-derived has trace plasma proteins	25 mL	Hemophilia A (Factor VIII deficiency)
Recombinant or plasma derived			
Human factor IX	Factor IX plasma-derived has trace plasma proteins	25 mL	Hemophilia B (Factor IX deficiency)
Recombinant or plasma derived			
Albumin	Albumin, some α-, β-globulins	(5%, 20%, or 25%)	Volume expansion, albumin replacement
Immune globulin	IgG antibodies	Varies	Hypo- or agammaglobulinemia; ITP
Rh immune globulin	IgG anti-D	1 mL	Prevention of hemolytic disease of the newborn due to D antigen; ITP
Antithrombin	Antithrombin	10 mL	Antithrombin deficiency
Recombinant factor VIIa	Factor VIIa	2.2 mL(1.2 mg)	Bleeding episodes for hemophilia A or B with inhibitors; bleeding episodes in patients with acquired hemophilia; Bleeding episodes in patients with congenital Factor VII deficiency
		8.5 mL(4.8 mg)	

RBC red blood cell, *WBC* white blood cell, *CMV* cytomegalovirus, *FFP* fresh frozen plasma, *ITP* idiopathic thrombocytopenic purpura, *PMN* polymorphonuclear leukocytes

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The goal of RBC transfusion is to maintain adequate tissue oxygen delivery (DO_2). Oxygen delivery is the product of cardiac output (CO) and arterial oxygen content (CaO_2).

with RBC transfusion would appear appropriate. Oxygen delivery (DO_2) is the product of cardiac output (CO) and arterial oxygen content (CaO_2). Arterial oxygen content is a function of Hb saturation, Hb concentration, and the amount of oxygen dissolved in the arterial blood.

$$DO_2\left(\text{mL/min}\right) = \text{CaO2}\left(\text{mL/dL}\right) \times \text{CO}\left(\text{L/min}\right) \times 10\,\text{dL/L, where}$$

$$CaO_2\left(\text{mL/dL}\right) = 1.34\left(\text{mL/g}\right) \times \text{Hb}\left(\text{g/dL}\right) \times SaO_2 + 0.003\left(\text{mL/dL/mmHg}\right) \times PaO_2\left(\text{mmHg}\right)$$

Red blood cell transfusion would be expected to increase oxygen delivery and thereby prevent tissue hypoxia and organ failure that is associated with anemia. However, tissue oxygen delivery by transfused allogeneic RBCs is not equivalent to that of native red blood cells, and oxygen extraction from the blood and cellular oxygen consumption (VO_2) and utilization do not reliably

Table 41.2 Complications of blood product transfusions

Hemolytic reactions
Hemoglobinuria, hemoglobinemia, fever, dyspnea, hypotension
Febrile nonhemolytic reactions
Fever, chills, tachycardia, headache, urticaria, rash, dyspnea
Generalized allergic/anaphylactic reactions
Angioedema, wheezing, upper airway edema, hypotension, shock, arrhythmias, death
Coagulopathy
Dilutional
Transfusion-transmitted infection
CMV, HIV, HBV, HCV, HTLV
Bacteremia
Graft-versus-host disease
Alloimmunization
Transfusion-related acute lung injury (TRALI)
Acute onset, bilateral infiltrates on chest radiograph, PaO_2/FiO_2 ratio < 300
Circulatory overload (TACO)
Dyspnea, pulmonary edema, congestive heart failure
Hypothermia
Metabolic abnormalities
Hypocalcemia, hyperkalemia

CMV cytomegalovirus, *HIV* human immunodeficiency virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HTLV* human T-cell lymphotrophic virus

increase following RBC transfusion. Stored RBCs have abnormal rheological properties (reduced deformability, increased adhesiveness, and aggregability) and biophysical profiles (low levels of 2,3-diphosphoglyerate and adenosine triphosphate (ATP)) that increase their oxygen affinity and impair oxygen release to the tissues.

A 2004 review of 18 clinical studies in adult ICU patients examining the effects of RBC transfusion on oxygen delivery and consumption found an increase in arterial oxygen content following RBC transfusion in all studies. Despite this increase in oxygen content, oxygen delivery was increased in only 14 of the studies (77%), and oxygen consumption in only 5 (27%). RBC transfusion in critically ill adults increased oxygen consumption *calculated* by the Fick equation but did not increase oxygen *utilization* when measured by indirect calorimetry (a more valid measure). Clearly, the reverse Fick principle calculation of VO_2 can be imprecise as it is an indicator of total body oxygen consumption as opposed to regional VO_2. At a minimum, these studies suggest that the transfusion of stored allogeneic RBCs does not consistently increase tissue oxygen availability.

The optimal RBC concentration is that which allows the greatest oxygen delivery at the lowest energy cost. Higher RBC concentrations increase blood viscosity, inhibit microvascular perfusion, and may raise systemic and pulmonary vascular resistance sufficiently to increase left ventricular and right ven-

tricular afterload respectively, increasing myocardial oxygen consumption. Red cell transfusion may increase right atrial pressure and stretch and interfere with autonomic reflexes leading to decreased heart rate and cardiac output. Increased circulating blood volume following transfusions in the nonbleeding patient may exacerbate fluid overload and increase myocardial work. Anemia of chronic disease may be adaptive and allow for optimal microvascular perfusion, oxygen extraction, and myocardial performance.

In contrast, significant blood loss results in hypovolemia and anemia. Acute or uncompensated anemia causes tissue hypoxia not only as a result of reduced oxygen-carrying capacity but also as a result of decreased cardiac output from deficient preload. To maintain oxygen delivery, tissues will compensate for reductions in oxygen carrying capacity by increasing regional blood flow. Most tissues are also able to increase oxygen extraction in response to decreased oxygen delivery. While the cardiac circulation has extremely high oxygen extraction ratio at rest (60–77%), its vasodilatory capacity in response to increased demand is limited. Under normal physiologic conditions, the heart relies on sympathetic discharge, increasing myocardial contractility, heart rate, and systemic vascular tone to further compensate for decreased oxygen delivery. When there is left ventricular dysfunction and/or coronary artery disease, the ability of the heart to increase cardiac output and coronary artery blood flow in response to severe anemia is compromised. Children with acquired or congenital heart disease who have myocardial dysfunction may be ill equipped to tolerate acute blood loss anemia, particularly with cyanotic lesions.

41.2.2 Indications

Many studies have been performed in attempt to determine the "optimal" hemoglobin concentration in the critically ill. The Canadian Critical Care Trial group's Transfusion Requirements in Critical Care (TRICC) trial reported that maintaining a Hb concentration between 7 and 9 compared to 10–12 g/dL resulted in comparable mortality rates in adult ICU patients, with younger (<55 years) and less severely ill patients half as likely to die when treated with the restrictive regimen. The CRIT study found that RBC transfusions were independently associated with longer ICU stays, hospitalizations, and increased mortality even after controlling for severity of illness. These results have been replicated in additional adult studies, which also demonstrate that worse outcomes are associated with higher numbers of transfused RBC units in a dose-dependent manner.

Transfusion trials of similar design have been repeated across many different disease states (i.e., gastrointestinal (GI) bleeding, sepsis, orthopedic conditions). All can be criticized for their study design, specifically lacking a "no transfusion group," yet all fail to find a survival advantage with use of liberal transfusion practices. However, data from patients with ischemic cardiovascular disease are conflicting. A recent meta-analysis of the effects of lower versus higher Hb levels on mortality in critically ill patients demonstrates no difference in mortality between groups nor in the chronic cardiovascular disease subgroup. Although a trend toward decreased mortality in the critically ill subgroup was found, there was also a nonsignificant trend toward increased mortality in the acute myocardial infarction subgroup.

In sum, it appears that maintaining hemoglobin concentration greater than 7–8 g/dL in the critically ill adult patient without concurrent cardiovascular disease is of no benefit. Even after controlling for severity of illness, there is an increase in morbidity and mortality associated with transfusion in critically ill adults.

It appears that maintaining hemoglobin concentration greater than 7–8 g/dL in the critically ill adult patient without concurrent cardiovascular disease is of no benefit and that there is an increase in morbidity and mortality associated with transfusion in these patients. However, patients with acute coronary insufficiency may benefit from increased transfusion support.

Data in critically ill children have mirrored the adult experience. Observational studies of critically ill children have found associations with worse clinical outcomes (increased days of oxygen use, mechanical ventilation, vasoactive agent infusion, and length of stay) and RBC transfusions, even after controlling for severity of illness. In the sentinel pediatric transfusion (TRIPICU) trial, 637 stable, critically ill children were randomized to a Hb concentration threshold of 7 or 9.5 g/dL for red blood cell transfusion. The study demonstrated fewer RBC transfusions in the restrictive group without an increase in adverse outcomes. Subgroup (surgical, sepsis, cardiac) analysis of the TRIPICU study consistently found no obvious benefit in the liberally managed subjects.

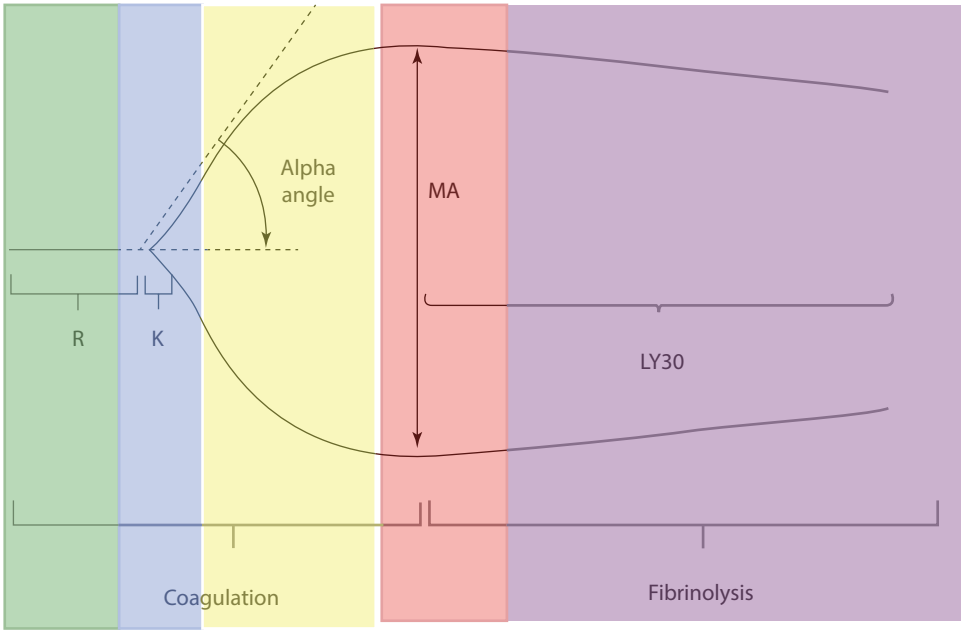
The 2018 Transfusion and Anemia Expert Initiative (TAXI) panel compiled and analyzed pediatric data (when available) and developed recommendations for RBC transfusion across different populations. The reader is referred to these manuscripts for a concise review of the evidence and recommendations.

Good practice statements from the TAXI consensus (Valentine 2018) conclude that in addition to the Hb level, physiologic variables and the clinical context and risk/benefit/alternatives should be considered in transfusion decision making. RBC transfusion is recommended for Hb levels <5 g/dL, with recommendation NOT to transfuse the hemodynamically stable critically ill child (or one at risk for critical illness) if their Hb is ≥7 g/dL. The expert consensus is that there is insufficient evidence to make a recommendation for transfusion when the Hb is ≥5 to 7 g/dL and that clinical judgment is required. The target posttransfusion Hb should not be for a "normal" Hb but for a Hb concentration between 7 and 9.5 g/dL. The authors recommend no transfusion for Hb ≥7 g/dL for children who are/or have: postoperative (excluding cardiac surgeries), respiratory failure (excluding severe pediatric ARDS), sepsis, nonlife-threatening bleeding, and those receiving continuous renal replacement therapy. Consideration for transfusion in children with acute brain injury should be for Hb 7–10 g/dL and 7–8 g/dL for those with oncologic disease or those requiring hematopoietic cell transplant.

The TAXI recommendations should help inform the bedside clinician in their transfusion decision making for the hemodynamically stable child. As there is no evidence to guide decisions in the unstable patient, our approach has been to reserve RBC transfusions for "clinical indications" and low Hb levels. Although the bedside intensivist can readily identify a "clinical indication" for RBC transfusion, we strive to maintain restrictive transfusion practices unless there is compelling evidence for end organ dysfunction and/or hemodynamic instability that cannot be mitigated with other measures. In general, we believe that RBC transfusion should be reserved for those children with anemia (purposefully not defined) and (1) acute hemorrhage or chronic blood loss resulting in hemodynamic instability; (2) clinical evidence for inadequate cardiac output unresponsive to volume replacement (or diuresis if appropriate as in those with congestive heart failure) and/or inotropic support and vasoactive agents; (3) complex cyanotic congenital heart disease with evidence for end organ dysfunction and/or inadequate oxygenation for their lesion; (4) hypoxic respiratory failure causing end organ compromise unresponsive to ventilatory supportive measures; (5) acute stroke or acute chest syndrome in sickle cell disease; and (6) bone marrow failure in hematologic/oncologic disease contributing to end organ dysfunction.

Modern transfusion medicine separates components from donated whole blood into plasma products (plasma, cryoprecipitate, platelets, coagulation factors, albumin, immunoglobulin) and red blood cells. Transfusion of component therapy maximizes use of a limited resource as multiple products can be

RBC transfusions should be reserved for children with anemia and: (1) acute hemorrhage or chronic blood loss resulting in hemodynamic instability; (2) clinical evidence for inadequate cardiac output unresponsive to volume replacement (or diuresis if appropriate as in those with congestive heart failure) and/or inotropic support and vasoactive agents; (3) complex cyanotic congenital heart disease with evidence for end organ dysfunction and/or inadequate oxygenation for their lesion; (4) hypoxic respiratory failure causing end organ compromise unresponsive to ventilatory support measures; (5) acute stroke or acute chest syndrome in sickle cell disease; and (6) bone marrow failure in hematologic/oncologic disease contributing to end organ dysfunction.



Thromboelastogram (TEG)				
Components	Definition	Normal Values	Problem with...	Treatment
R Time	Time to start forming clot	5 - 10 minutes	Coagulation Factors	FFP
K Time	Time until clot reaches a fixed strength	1 - 3 minutes	Fibrinogen	Cryoprecipitate
Alpha angle	Speed of fibrin accumulation	53 - 72 degress	Fibrinogen	Cryoprecipitate
Maximum Amplitude (MA)	Highest vertical amplitude of the TEG	50 - 70 mm	Platelets	Platelets and/or DDAVP
Lysis at 30 Minutes (Ly30)	Percentage of amplitude reduction 30 minutes after maximum amplitude	0 -8Z	Excess Fibrinolysis	Tranexemic Acid and/or Aminocaproic Acid

Fig. 41.1 Sample thromboelastogram. (Figure Courtesy of Salim Rezaie. R.E.B.E.L. EM. ► https://rebelem.com/wp-content/uploads/2019/03/Thromboelastogram-TEG.png)

derived from a single donor unit. Development of point of care testing (i.e., thromboelastography) has aided in directing specific replacement component therapy for the bleeding patient, helping to avoid transfusion of products that will not support the intended benefit (Fig. 41.1). Despite the centrifugal separation of red cells, it is important to remember that the RBC unit is not free of all plasma, and therefore contains contaminating leukocytes, platelets, cellular components, and bioactive substances. Residual leukocytes may incite hemolysis resulting in leakage of potassium, toxic oxygen radicals, and destructive enzymes into the storage media and have been implicated in posttransfusion immunosuppression and postoperative infections. High levels of cytokines (IL-1, IL-8, TNF-α) found in the storage media are thought responsible for febrile transfusion reactions. Additional blood processing (leukoreduction, irradiation, washing) is employed to mitigate the "storage lesion" and decrease transfusion complications. In addition, volume depleted units are commonly used in neonates and may be requested for patients with fluid overload and/or renal failure.

Whole blood contains RBCs, leukocytes, platelets, plasma, and proteins and is transfused to increase both red blood cell mass and plasma volume.

Whole-blood transfusions were initially utilized for those suffering acute massive hemorrhage on the battlefield and for nonmilitary victims of trauma, where replacement of the individual's blood volume is often required. Whole blood has been utilized for transfusion in specific types of pediatric surgery such as cardiac surgery requiring cardiopulmonary bypass and complex craniofacial remodeling. Although there are strong advocates for its use in the operating room, there are limited data to support its clinical benefit over the use of component therapy. Individual trauma and surgical centers may have site-specific whole-blood transfusion protocols, but whole blood is not available in many centers.

Most tertiary care centers have developed massive transfusion protocols that can be employed in cases of unexpected severe bleeding when large volume transfusion is required as in cases of trauma, solid organ transplant, obstetric emergencies, and/or surgical complications. "Massive transfusion" can be defined in multiple ways, but essentially is considered when there is required replacement of a patient's blood volume (or > 10 RBC units) in a 24 hour period, or > 4 units in <4 hours, or in settings where continued profuse bleeding is expected (typically quantified as >150 mL/min in adults). Initiation of a massive transfusion protocol alerts the blood bank to this unexpected need and allows for efficient ordering, processing, and dispatching of required blood component therapy in an ongoing fashion to the ICU, emergency department, operating room, or labor and delivery that balances RBC and coagulant product utilization. Although the optimal ratio can be debated, massive transfusion protocols typically include preparation and delivery of product in a ratio of 1:1 for RBCs and plasma or 1:1:1 (RBCs, plasma, and platelets).

41.2.3 Alloimmunization

Alloimmunization (or isoimmunization) occurs when disparities between red cell antigens in the blood donor and blood recipient exist, and antibodies to these antigens are produced in the blood transfusion recipient. The patient (blood recipient) becomes alloimmunized, and immune-mediated hemolysis will occur following any later exposure to the sensitizing donor antigens. Alloimmunization is estimated to complicate 2.6% of RBC transfusions in the general population. It not only limits the effectiveness of the RBC transfusion but can also cause life-threatening delayed hemolytic transfusion reactions and limit subsequent transfusion therapy. Alloimmunization occurs more frequently in patients who receive multiple RBC transfusions throughout their life and can limit matching of tissue allografts. Cross-matching blood for patient transfusions is challenging in alloimmunized patients and can limit both the amount and the speed at which blood products are available for transfusion.

41.2.4 Storage

The need to support a wounded military gave rise to the creation of modern transfusion medicine. In 1914, the media used to store RBCs were citrate anticoagulant and dextrose. Today, anticoagulant and nutrient solutions are added; commonly used is citrate phosphate dextrose adenine (CPDA) that preserves ATP levels, increasing the lifespan of the stored product from 15 to 35–42 days. Nonetheless, RBCs stored *ex vivo* still undergo biochemical and morphological changes (RBC storage lesion) that hinder RBC transport and oxygen deliv-

ery. During storage, the erythrocyte is deprived of energy and a series of morphological changes occur including the loss of the normal biconcave disc shape with crenation and spicule formation producing echinocytes. The swelling of echinocytes forms spheroechinocytes. Eventually, the cell sheds its spicules as lipid vesicles and spherocytes are formed. Spherocytes, with their low surface to volume ratio, are unable to deform and traverse the microcirculation, and their increased osmotic fragility results in hemolysis. In addition, endogenous antioxidants are lost resulting in damage to cytoskeletal proteins and membrane phospholipids. Hemoglobin is also converted to methemoglobin which cannot bind oxygen. Finally, stored erythrocytes are depleted of 2,3-diphosphoglycerate (2,3-DPG) increasing oxygen affinity and, thus, hindering off-loading of oxygen to tissues.

Twenty percent of RBC units held in American blood banks and transfusion centers are 28 days old or older, with units of relatively rare blood types (i.e., O−) more consistently older. Multiple studies have found an association between increased mortality, increased length of stay, multiple organ system failure, increased infections, and impaired tissue oxygen utilization with the length of RBC storage. In an analytic cohort analysis of the TRIPICU study of critically ill pediatric patients, storage duration of greater than 14 days was independently associated with increased multiple organ dysfunction syndrome (MODS) and storage >21 days was associated with higher mortality. A large, multicenter, prospective, randomized trial (ABLE trial) in critically ill adults compared the impact of storage duration on mortality. Patients were randomized to receive blood of <8 days storage compared to standard issue. There was no significant difference in 90-day mortality (the primary outcome) or secondary outcomes between groups. A multicenter, double-blind, superiority, randomized controlled trial comparing storage age of RBCs in critically ill children (≤7 days vs. standard issue) has just been completed. It found that among critically ill pediatric patients, the use of fresh red blood cells did not reduce the incidence of new or progressive multiple organ dysfunction syndrome (including mortality) compared with standard-issue red blood cells.

41.2.5 Administration

Pediatric blood volume is approximately 70–75 mL/kg, and 3 mL/kg pRBCs generally increases a child's hemoglobin by 1 g/dL.

In adults, the average blood volume is 60–66 mL/kg; one unit of RBCs generally raises the Hb by 1 g/dL. Pediatric blood volume is approximately 70–75 mL/kg, and a 3 mL/kg RBC transfusion generally increases the Hb of a child by 1 g/dL. Adoption of blood conservation practices had led to a change from the historic 2 units of RBC transfused to adults to transfusion in 1 unit aliquots. It is now recognized that the goal of RBC transfusion is not to return the patient's Hb to normal but rather to raise it above a critically low value. The potential for adverse outcomes following large volume RBC transfusion is greatest in the smallest patient, and transfusion dose is weight-based and not unit-based in pediatrics. Pediatric patients without ongoing and severe bleeding should be transfused in doses of 10 mL/kg. Our protocol is to give each RBC transfusion over 3–4 hour to the stable adult or pediatric patient. In the hemodynamically unstable patient, our practice is generally to infuse an aliquot of the total volume as a bolus and the remainder over 1–2 hours if the patient's hemodynamics responds.

Although general guidelines have been discussed, appropriate treatment of the critically ill child demands a careful, individualized approach. It is important to note that the volumes as well as the hematocrits of units of RBCs may vary significantly within and between institutions. It is also important to take

into account the average hematocrit of a particular unit and to be aware of the actual volume that will be given when transfusing a "unit." At our institution, the volume of one unit of filtered RBCs is typically between 330 and 420 mL with a hematocrit between 50% and 55%. A unit of washed filtered red cells is between 200 and 250 mL with the hematocrit approximately 75–80%. Some blood banks concentrate RBCs for neonates, a process that raises the hematocrit of the volume transfused. Our blood bank automatically utilizes volume-depleted RBC units (hematocrit of 70–75%) for transfusions in children less than 3 years of age. Only upon special request, and if specific criteria are met, will volume-depleted units be utilized for patients over 3 years.

There are a number of formulas available to predict the volume of transfused red cells needed to achieve a particular hemoglobin or hematocrit. The traditional formula for RBC replacement is:

The traditional formula for RBC replacement is: volume of RBC (mL) = EBV (mL) × (Desired Hct (%) – Actual Hct (%))/Hct of RBCs (%).

$$\text{Volume of pRBCs (mL)} = \text{EBV (mL)} \times \frac{\text{Desired Hct(\%)} - \text{Actual Hct(\%)}}{\text{Hct of pRBCs(\%)}}$$

Where pRBCs = packed red blood cells, the EBV = estimated blood volume, Hct = hematocrit, and the Hct of RBCs is usually 55–70%. Concern has been raised that this formula underestimates the required volume, with an alternative formula proposed:

$$\text{Volume of pRBCs to transfuse (mL)} = 4.8 \times \text{weight (kg)} \times \text{desired rise in Hb (g/dL)}$$

$$\text{Volume of pRBC to transfuse (mL)} = 1.6 \times \text{weight (kg)} \times \text{desired rise in Hct (\%)}$$

The above formulas apply to red blood cell units with a median hematocrit of 70% (hemoglobin of 23 g/dL). Depending upon the average hematocrit of the pRBC units at a given institution, the appropriate formula can be used to calculate the volume of pRBCs to be transfused. Practitioners should always keep in mind that RBC transfusions are not without risk. Infection, transfusion reactions, acute lung injury, and alloimmunization are among the associated complications and will be discussed later in the chapter.

41.3 Platelet Transfusions

41.3.1 Indications

Primary hemostasis is dependent upon platelets. Platelet transfusions are indicated for patients who are compromised by decreased platelet production, increased platelet destruction, and/or platelet dysfunction. General indications for platelet transfusions include (1) acute hemorrhage associated with thrombocytopenia, (2) prophylaxis in nonbleeding patients with severe thrombocytopenia, and (3) prophylaxis in thrombocytopenic patients requiring surgical interventions. Platelet transfusion should also be used in children with normal platelet counts who experience (1) bleeding in association with a qualitative platelet defect or (2) excessive bleeding while undergoing cardiopulmonary bypass or extracorporeal membrane oxygenation (ECMO). Children undergoing ECMO are typically maintained with a platelet count greater than 30–50,000/μL if they are not bleeding. Children undergoing surgery with cardiopulmonary bypass are not generally given platelet transfusions postoperatively unless there is active bleeding and a platelet count less than 50,000/μL.

General indications for platelet transfusions include (1) acute hemorrhage associated with thrombocytopenia, (2) prophylaxis in nonbleeding patients with severe thrombocytopenia, and (3) prophylaxis in thrombocytopenic patients requiring surgical interventions.

Platelet transfusion is generally not indicated in children with idiopathic thrombocytopenic purpura (ITP) unless there is life-threatening hemorrhage since transfused platelets will, like endogenous platelets, also be destroyed by immune mechanisms. Other treatment modalities are used. Platelet transfusions are contraindicated in thrombotic thrombocytopenic purpura (TTP) where the infused platelets may contribute to ongoing thrombosis.

The risk of spontaneous hemorrhage is highest at platelet counts below 5000/μL, and platelets are generally transfused for this level of thrombocytopenia whether or not the patient is bleeding. Platelet counts between 5000 and 10,000/μL are often associated with hemorrhage secondary to trauma, invasive procedures, or ulceration. Bleeding tendency is variable with platelet counts between 10,000 and 50,000/μL. In the absence of bleeding, but in anticipation of a surgical procedure, the typically accepted threshold for platelet transfusion is 100,000/μL. A study of thrombocytopenia in patients with acute leukemia used a threshold of 10,000/μL for prophylactic transfusions instead of 20,000/μL; this approach resulted in fewer transfusions overall and no difference in rates of severe bleeding, remission, or mortality. Therefore, using 10,000/μL of platelets as a guideline for prophylactic transfusions in such children appears appropriate. For life-threatening bleeding in any patient, the platelet count should be maintained above 100,000/μL.

Neonatal alloimmune thrombocytopenia (NAIT) is the leading cause of severe thrombocytopenia in the fetus and neonate. A consequence of maternal antibodies directed against disparate paternally derived antigens on the fetal platelet, NAIT may produce no symptoms or present with bleeding of variable severity including intracranial hemorrhage. Symptomatic or severe thrombocytopenia (e.g., <30,000/μL) should be treated initially with random donor platelets matched to the neonate as well as intravenous immune globulin (IVIG), which may prolong the survival of the transfused platelets. Washed maternal platelets, which typically require several days to obtain, may be used if the neonate is transfusion dependent for an extended period of time.

41.4 Types of Platelet Units and Storage Procedures

Difficulties with platelet clumping, bacterial contamination, and storage conditions made platelet transfusions unavailable until the late 1960s except when given in fresh whole blood. It was the development of gas-permeable plastic that allowed platelets to be safely separated from whole blood and then to be stored at room temperature (20–24 °C) for up to 5 days under constant agitation to prevent clumping. The shorter shelf life of platelets is due to their storage at room temperature, which increases the risk of bacterial growth. Platelets cannot be refrigerated as this severely compromises posttransfusion platelet survival due to platelet activation and clumping.

Platelet units are available as platelet concentrates, typically obtained from 5 to 7 whole-blood donations, or single donor platelets collected from platelet apheresis. To produce platelet concentrates, RBCs are separated from whole blood using a "soft-spin" technique; the platelets then undergo a "hard-spin" separating them out of the plasma forming a platelet concentrate suspended in approximately 50 mL of plasma. Each unit contains approximately 0.55–0.8 × 10^{11} platelets. With platelet apheresis, multiple units of platelets can be collected from a single donor, thereby reducing the alloimmunization that can result from multiple donor exposures. Single donor platelets are more expensive than platelet concentrates and are typically reserved for patients requiring HLA-matched units.

Like RBC transfusions, platelet transfusions also carry risks of infection and alloimmunization. In December 2002, the College of American Pathologists mandated that platelet products be inspected for bacterial contamination. The accepted standard for testing is by culturing the platelet components and waiting 24 hour for the results before releasing the platelets for transfusion. Platelet components also contain white blood cells which may cause allergic reactions. With the advent of universal leukoreduction, the incidence of these effects following platelet transfusions has greatly decreased (see below). Approximately one-half of patients receiving platelet concentrates develop alloimmunization. Alloimmunization occurs when antibodies in the recipient serum react with HLA class I antigens on donor platelet membranes, decreasing platelet survival and function. The patient's history of immunogenic stimuli (blood products and pregnancies) and genetic characteristics appear to determine whether alloimmunization will occur. Leukoreduction of platelet products has also significantly reduced the occurrence of alloimmunization from approximately 13 to 3% (see below). If a patient is alloimmunized, the current standard of care is to utilize either HLA-matched or cross-matched single donor platelets (SDP) for future platelet transfusions.

41.5 Administration

Typically, one unit of platelets is transfused per 10 kg body weight in adults. The dosage for infants and children is 10 mL per kg, which raises the platelet count by approximately 50,000/μL. Six units of platelets in the "standard" adult patient should raise the platelet count by about 30,000/μL 1 hour after the infusion. Each unit of platelets typically raises the platelet count by approximately 5000–10,000/μL in adults. Platelet transfusions are considered successful if they stop bleeding, and if a posttransfusion corrected count increment of greater than 10,000/μL of platelets is achieved.

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Refractoriness to platelet transfusions, demonstrated by a lack of significant increase in platelet count following transfusion, is a major concern for patients with hematological diseases requiring continued platelet support. Both immune (alloimmunization) and nonimmune processes contribute to platelet refractoriness. Nonimmune causes of platelet refractoriness include infection, fever, consumption (disseminated intravascular coagulation), splenomegaly, cytotoxic drugs, antifungals (amphotericin), and antibiotics. Approximately one-third of transfused platelets are sequestered by the spleen, which may compound a poor response to platelet transfusions.

41.6 Fresh-Frozen Plasma

Clotting factor deficiencies occur commonly in the critically ill child. Coagulation proteins are often diminished in the setting of trauma secondary to dilution following massive RBC transfusion and the blood loss from the traumatic injury. Furthermore, tissue thromboplastins and plasminogen activators are released when tissue is devitalized, triggering the coagulation cascade and the consumption of coagulation factors. Trauma and burn patients with extensive tissue injury often develop disseminated intravascular coagulation (DIC) during which their coagulation proteins are consumed. Hypothermia, which often develops in these patients, inhibits serine protease activity leading

to decreased activation of coagulation factors and prolongation of the prothrombin time (PT) and activated partial thromboplastin time (aPTT). Severe sepsis may also activate the coagulation cascade causing a consumptive coagulopathy and/or DIC.

Replacement of coagulation proteins can be accomplished by the infusion of fresh frozen plasma (FFP). FFP is derived from whole-blood donations placed at or below −18 °C within 8 hour of collection and is viable for up to 12 months. Fresh frozen plasma contains coagulation factors II, VII, IX, and X (1 mL = 1 unit of factor activity) and naturally occurring inhibitors (Proteins C and S). The volume of one bag of FFP is about 200–250 mL. Larger volumes (400–600 mL) are collected via single donor plasmapheresis. In older children, single donor units are preferred over the use of two bags of FFP since this approach limits donor exposure.

Indications for the use of FFP in children include (1) support during episodes of DIC with severe bleeding, (2) factor replacement when concentrates are not available, (3) therapeutic plasma exchange in circumstances such as TTP, and (4) warfarin reversal to stop active bleeding or before surgery. FFP should not be used as a volume expander.

Indications for the use of FFP in children include (1) support during episodes of DIC with active bleeding, (2) factor replacement when concentrates are not available, (3) therapeutic plasma exchange in circumstances such as TTP, and (4) warfarin reversal to stop active bleeding or before surgery. FFP should not be used as a volume expander. If the PT >1.5 times the midpoint of the normal range, or the aPTT >1.5 times the upper limit of the normal range, FFP should be considered if bleeding is present, or prior to an invasive procedure. (It is important to recognize that reference ranges for coagulation factors vary with age, and adult standards do not apply for pediatric patients.) For the pediatric patient, the typical dose of FFP is 10–15 mL/kg. Of note, every 5–6 units of platelets contain a plasma protein volume equivalent to one bag of FFP, so that when platelets are also administered, a smaller volume of FFP is needed.

Adverse effects of FFP are volume overload, anaphylaxis, and transfusion reactions. Shortening of coagulation times is variable, and normalization may be incomplete so that follow up testing should always be performed. Repeated dosing of FFP may be required, which contributes to the potential for volume overload.

41.7 Prothrombin Complex Concentrate

Although available for decades in Europe to reverse vitamin K antagonist related bleeding, prothrombin complex concentrates were not approved for use until 2008 in Canada and 2013 in the United States for safety concerns related to venous thromboembolism. Prothrombin complex concentrates (PCC) are available as 3 Factor PCC – containing Factors II, IX, X and Proteins C and S; or 4 Factor PCC – also containing Factor VII. The primary indication for PCC is reversal of vitamin K antagonist, and its benefit is lower volume of administration. PCC are increasingly being used as off-label therapy in infants and children with severe bleeding. Some case reports suggest PCC to be effective as replacement of coagulant factor deficiency, but there are little data on PCC effectiveness as to vitamin K antagonist reversal in children. A 2017 systematic review and meta-analysis in neonates and infants found insufficient evidence to allow for a recommendation on the use of PCC in neonates and infants.

41.8 Cryoprecipitate

Cryoprecipitate contains Factor VIII, von Willebrand factor (vWF), fibrinogen, Factor XIII, and fibronectin and is used as replacement therapy when these proteins are low in the setting of active bleeding or in preparation for an invasive or surgical procedure.

Cryoprecipitate is the cold precipitable protein fraction obtained from FFP thawed at 1–6 °C. It is resuspended in 9–16 mL of residual plasma supernatant, refrozen, and stored at −18 °C for up to 1 year. Cryoprecipitate contains Factor VIII, von Willebrand factor (vWF), fibrinogen, Factor XIII, and fibronectin and is used as replacement therapy when these proteins are low in the setting of active bleeding or in preparation for an invasive or surgical procedure. Hypofibrinogenemia may be secondary to dilution after a massive transfusion or may occur in the setting of DIC. Fibrinogen levels >100 mg/dL are adequate for hemostasis, and cryoprecipitate should only be given if the hypofibrinogenemia is associated with bleeding or bleeding risk. Dysfibrinogenemia, also in the context of bleeding or surgery, is another indication for cryoprecipitate. Cryoprecipitate can be similarly used in Factor XIII deficiency if Factor XIII is unavailable. Cryoprecipitate can also be used for patients with von Willebrand disease refractory to deamino-D-arginine vasopressin (DDAVP), when DDAVP is not indicated, and/or virally inactivated plasma-derived Factor VIII concentrate is not available. Cryoprecipitate is no longer used for children with Factor VIII deficiency because Factor VIII concentrates are widely available.

The amount of cryoprecipitate necessary to correct a deficit of fibrinogen can be calculated according to the formula: desired increment in g/L = (0.2 × number of bags)/plasma volume (liters). A good rule of thumb is to transfuse one bag of cryoprecipitate for every 5 kg of body weight. The half-life of fibrinogen is 3–5 days with about 50% recovery of transfused product. The specific content of vWF in a single bag of cryoprecipitate is unknown; the standard dose of cryoprecipitate to treat von Willebrand disease is one bag per 10 kg of body weight.

41.9 Granulocyte Transfusions

For over 70 years, there has been great interest in polymorphonuclear leukocyte (PMN) transfusions for the treatment and prevention of life-threatening infections in neutropenic patients. Initially, the inability to obtain adequate numbers of PMNs and limited leukapheresis techniques hindered the use of PMN transfusions. However, treating donors with granulocyte colony-stimulating factor (G-CSF) and corticosteroids prior to leukapheresis has been found to elevate donor PMN counts and to increase PMN collection yields. The most cost-effective regimen for increasing PMN mobilization in donors appears to be a single dose of G-CSF, 450 μg subcutaneously, plus dexamethasone 8 mg po 12 hours prior to leukapheresis. Most transfusion centers rely on continuous-flow centrifugation leukapheresis for granulocyte collection. The current goal is to transfuse the PMNs immediately after leukapheresis; yet there is some evidence to suggest that granulocytes can be safely stored for up to 24 hour. At this time, there are no controlled trials to guide optimal storage duration.

The transfusion of PMNs has been found to restore peripheral blood PMN counts to the normal range in neutropenic recipients. The transfused granulocytes also demonstrate normal function, as evidenced by their ability to migrate

to tissue sites *in vivo* (as measured by the buccal PMN response). The effectiveness of granulocyte transfusion therapy in treating infections in severely neutropenic patients remains in question. The literature is composed of uncontrolled studies with small sample sizes, variable dose and quality of PMNs, and variable underlying diseases, treatments, and types of infections. Taking these limitations into account, one meta-analysis concluded that 62% of subjects with bacterial sepsis benefited from granulocyte therapy; 71% of patients with fungal infections responded. A prospective phase I/II study of patients with severe neutropenia receiving granulocyte transfusions for uncontrolled sepsis found that infections cleared in 19 of 30 patients. Fourteen of seventeen patients with bacteremia recovered, but only 5 of 13 patients with fungemia cleared their infection. A multicenter prospective study published in 2015 found no difference in outcome between the group receiving granulocyte transfusions and the control group, but low accrual decreased the power of the trial to detect a difference.

Most transfusion reactions secondary to granulocyte transfusions are similar to those associated with other blood products. Severe reactions (hypotension, pulmonary infiltrates, and respiratory distress) occur in 10–15% of transfusions in prospective trials, especially when granulocytes are given concomitantly with amphotericin B. As with RBC and platelet transfusions, alloimmunization is also a concern. The testing for antibodies to ABO antigens and for leukoagglutination, as well as the irradiation of PMN products prior to transfusion, has decreased the incidence of these problems.

41.10 Blood-Derived Albumin

Albumin is produced by the liver and is the most abundant protein in serum, making up approximately 50% of all proteins and has a 3 week half-life. Albumin is the main determinant of oncotic pressure in the blood (responsible for 80% plasma oncotic pressure), regulating plasma and tissue fluid volumes. Albumin is used for volume expansion and colloid replacement. When infused to facilitate movement of interstitial fluid into the blood stream, blood-derived albumin infusion has a half-life of 12–16 hours. However, in cases of the systemic inflammatory response syndrome (SIRS) and/or capillary leak, the half-life of albumin can be shortened dramatically.

Albumin is derived from pooled human plasma, is pasteurized at 60 °C for 10 hours, and is not type-specific; it can be given regardless of the patient's blood type. Typically, albumin is available in 5%, 20%, and 25% preparations. The oncotic pressure of 5% albumin is similar to that of plasma. Solutions with higher albumin concentrations are hyperosmotic. All preparations contain sodium, 130–160 mEq Na+/L. Higher percentage albumin solutions are typically given for severe hypoalbuminemia with fluid overload and 5% albumin given for hypovolemic patients with ongoing protein losses.

The dose to obtain a serum albumin ≥2.5 g/dL can be calculated by the formula:

$$\text{Dose}(\text{g}) = \begin{bmatrix} \text{desired albumin concentration}\,(\text{g/dL}) \\ -\text{actual albumin concentration}\,(\text{g/dL}) \end{bmatrix} \times \text{plasma volume}\,(0.8 \times \text{kg}).$$

Typical dosing of 5% albumin is 5–10 mL/kg over 30–60 minutes. Typical dosing of 25% albumin is 0.5–1.0 g/kg given over 60 minutes. Albumin infusions are generally well tolerated although they can have immediate allergic-type reactions, and higher preparations given rapidly have been noted to cause

hypotension. In general, 25% albumin is given for replacement when albumin levels are <2.0–2.5 g/dL. Although oncotic pressure appears to be maintained with albumin levels >2.0 g/dL, critical lower thresholds have not been determined.

Albumin solutions are generally given in the emergency treatment of hemorrhagic shock and in the acute management of severe burns. Other indications include (1) acute hypotension with acute or chronic liver failure or following paracentesis for ascites; (2) maintenance of blood volume during plasma exchange procedures or therapeutic phlebotomy for polycythemia; (3) in combination with diuretics to induce diuresis in fluid overload and protein-losing enteropathy or nephropathy, or acute-on-chronic liver failure; (4) to elevate protein levels in select patients with critical illness and/or nutritional failure and/or ongoing losses (chest, mediastinal and/or peritoneal drainage); and (5) cardiovascular collapse secondary to hypovolemia during extracorporeal circulation.

Albumin is generally given in the emergency treatment of hemorrhagic shock with hypovolemia, and in the acute management of burns. Other indications include (1) acute hypotension with acute or chronic liver failure or following paracentesis for ascites, (2) maintenance of blood volume during plasma exchange procedures or therapeutic phlebotomy for polycythemia, (3) in combination with diuretics to induce diuresis in fluid overload and protein-losing enteropathy or nephropathy, or acute-on-chronic liver failure, (4) to elevate protein levels in select patients with critical illness and/or nutritional failure and/or ongoing losses (chest, mediastinal and/or peritoneal drainage), and (5) cardiovascular collapse secondary to hypovolemia during extracorporeal circulation.

The use of albumin for fluid resuscitation of critically ill patients with nonhemorrhagic hypovolemia has long been subject to debate. The Cochrane Database of Systemic Review has published multiple analyses over the years, most recently updating their 2013 review in 2018 which examined the effect of colloid (albumin, dextran, starches, FFP) versus crystalloid solutions on patient survival, need for blood transfusion or renal replacement therapy, and adverse events (mainly allergic reactions). Their review was focused on critically ill patients with trauma, burns, or medical conditions such as sepsis; neonates were excluded. Sixty-nine studies with over 30,000 participants were examined, and the authors concluded that there is little to no difference on mortality, blood product use, or renal replacement therapy with use of colloid vs. crystalloid.

Current literature suggests that albumin and crystalloid are clinically equivalent for intravascular volume replacement for the critically ill patient. In light of the fact that the cost of albumin is approximately 30 times greater that of crystalloid fluids and is in short supply, the use of albumin over crystalloid fluid to increase intravascular volume in the nonbleeding patient without hypoproteinemia or burns is not supported by the literature. Our current practice is to avoid the use of albumin as resuscitative fluid unless there are ongoing losses as in burn or cardiac surgical patients. Additional trials are underway which may further help inform practice.

41.11 Intravenous Immune Globulin

Intravenous immune globulin (IVIG) is most commonly administered as replacement therapy in immune-globulin-deficient patients or to suppress an autoimmune or inflammatory process in an immunologically competent individual. For treatment of immune deficiency, IVIG replaces missing antibodies. For immunomodulation, the mechanism is not entirely clear. It is thought that IVIG binds to mononuclear phagocyte Fc receptors and competitively inhibits Fc receptor binding to cell associated antibodies, preventing phagocytosis. IVIG is composed of four subclasses of IgG, with IgG1 being the major component. IgG1 is involved in virus inactivation, complement activation, and tissue protection. Other postulated actions of IVIG include increased complement absorption, downregulation of immunoglobulin production, neutralization of viruses, enhancement of suppressor cells, inhibition of lymphocyte proliferation, and decreased production and activity of IL-1.

IVIG is most commonly administered as replacement therapy in immune-globulin-deficient patients or to suppress an autoimmune or inflammatory process in an immunologically competent individual.

IVIG is derived from pooled human plasma (hundreds to thousands of donors) that has been isolated by the Cohn-Oncley process (cold ethanol fractionation). The manufacturing of IVIG entails sequential precipitation and fractionation to isolate IgG from plasma proteins, although traces of IgA, IgM, IgD, and IgE persist. In most IVIG products, ethanol is then removed by freeze-drying, producing stable intermediates and insoluble IgG aggregates that require further processing. Each IVIG preparation has different properties depending upon the approach to processing (i.e., solvent detergent, pasteurization, nanofiltration, ultrafiltration, etc.), but each is considered equivalent in efficacy. All products undergo virus inactivation or removal, but the potential for viral transmission still exists. Seven polyclonal IVIG preparations have U.S. Food and Drug Administration (FDA) approval and are available in the United States. Additionally, four hyperimmune products are indicated for the treatment of cytomegalovirus, hepatitis B (HBIG), and varicella-zoster and for Rh prophylaxis (Rhogam).

The most common uses for IVIG in children are (1) primary or secondary humoral immunodeficiency states; (2) hematologic diseases such as ITP; (3) opportunistic infection prophylaxis in hematopoietic cell transplant recipients; (4) neonatal alloimmune thrombocytopenia or neonatal sepsis (by providing immature infants with antibodies); (5) Kawasaki disease; or (6) Guillain-Barre syndrome. Diseases with less clear indications include intractable seizures, myasthenia gravis, inflammatory myopathy, systemic lupus erythematosus, antiphospholipid antibody syndrome, rheumatoid arthritis, inflammatory bowel disease, systemic vasculitis, chronic idiopathic urticaria, asthma, and bullous pemphigoid. The use of IVIG as an immunomodulator in septic states has generated great interest. It is speculated that IVIG may inactivate toxins, stimulate leukocyte and serum bactericidal activity, interfere with cytokine effects, and prevent excessive complement activation although there is no proven efficacy.

Headaches, myalgias, nausea, vomiting, and facial flushing occur during 10% of IVIG infusions and may be alleviated by slowing or stopping the infusion. Acetaminophen, diphenhydramine, and/or hydrocortisone prior to the infusion may lessen these reactions. Aseptic meningitis, transient hemiplegia, acute and chronic renal failure (with pre-existing renal disease), and anaphylaxis (with selective IgA deficiency) have been reported. For treating immunodeficiency, 400–600 mg/kg IV Q3–4 weeks is the typical maintenance dose, with a goal trough serum IgG level > 500 mg/dL. ITP is treated with higher doses of IVIG, generally 1 g/kg IV. Some of the complications noted above are more frequent with therapy at this dose. The rate of infusion depends upon the preparation and the patient's tolerance of the infusion, with rates ranging from 0.03 to 0.13 mL/kg/min. Preparations with a higher osmolality or sucrose concentration are infused more slowly. IgA-deficient patients may have anti-IgA antibodies and, as such, can have a severe reaction to IVIG. Therefore, before administering IVIG, clinicians should consider measuring serum levels of IgA. If patients are IgA deficient, they should receive an IVIG product with the lowest IgA content possible.

41.12 Activated Protein C

Protein C is a vitamin K-dependent glycoprotein synthesized by hepatocytes. Protein C circulates in its inactive form until it is activated by the thrombin-thrombomodulin complex on vascular endothelial cells. Activated Protein C has three main effects: (1) antithrombosis by inactivation of Factors Va and VIIIa; (2) antiinflammatory effects secondary to a variety of mechanisms (blockage of cytokine formation, selectin activity, and NF-κB translocation);

and (3) enhancement of fibrinolysis by the inactivation of plasminogen activator inhibitor-1 (PAI-1), and inhibition of thrombin-activated fibrinolysis inhibitor (TAFI). Severe sepsis is known to cause acquired Protein C deficiency and lower levels have been associated with an increased morbidity and mortality in septic patients. Severe sepsis may also impair the conversion of Protein C to its activated form.

Knowledge of the role activated Protein C plays in sepsis prompted trials in which recombinant human activated Protein C (rhAPC), also known as activated drotrecogin alfa, was infused into septic patients. A study conducted in adults, the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial, demonstrated a decrease in 28-day all cause mortality in patients who received rhAPC. An open-label study of pediatric patients with purpura-fulminans-associated meningococcemia demonstrated decreased morbidity and mortality in rhAPC-treated patients. In view of these promising studies, a randomized, double-blind, placebo-controlled trial of rhAPC in pediatric patients with sepsis was performed. This investigation was stopped after an interim analysis revealed treatment futility and an increase in central nervous system hemorrhage in treated subjects. The PROWESS-SHOCK trial, a follow up to the original study, also did not find a mortality benefit in treated subjects. Since no benefit was established, and later trials demonstrated increased risk of serious bleeding and death, activated drotrecogin alfa (Xigris) was taken off the worldwide market in October 2011 and all clinical trials involving the drug have been discontinued.

41.13 Recombinant Factor VIIa

Recombinant Factor VIIa (rFVIIa) is a form of blood Factor VII manufactured by recombinant DNA technology. Recombinant Factor VIIa is a vitamin K-dependent glycoprotein indicated for the treatment of bleeding in patients with hemophilia and inhibitors or congenital Factor VII deficiency. Off-label use of rFVIIa for uncontrolled, severe bleeding in patients without hemophilia has grown. A 2005 consensus panel of experts concluded that the use of rFVIIa in nonhemophiliacs is "appropriate in limited circumstances: (1) cardiac, thoracic, aortic, or spinal surgery; hepatic resection; hysterectomy; or postpartum bleeding (when significant clotting factor replacement has failed); (2) for severe multiple trauma (only if surgery and substantial blood replacement are unsuccessful); and (3) nontraumatic intracranial bleeding (only if less than 4 hours has elapsed since symptom onset or if traumatic bleeding is associated with anticoagulant use and hematoma expansion)." The use of rFVIIa increases risk for significant thromboembolic complications including myocardial infarction, pulmonary embolus, cerebral vascular accident, and deep venous thrombosis. Doses of 20–40 mcg/kg are typically administered for nonemergent indications with 41–90 mcg/kg recommended for use in emergent, off-label situations. The expert panel described above did not address the use of rFVIIa in children. Case reports and institutional database reviews indicate that rFVIIa controls bleeding and reduces blood product transfusions. Significant thromboembolic complications have been reported following rFVIIa administration. A mortality benefit has not been demonstrated in either adults or children treated with rFVIIa. High quality data for off-label use in children are lacking. We utilize rFVIIa on a case-by-case basis for children undergoing cardiac surgery and/or extracorporeal membrane oxygenation with life-threatening hemorrhage unresponsive to surgery and blood product replacement.

41.14 Blood Processing

41.14.1 Leukoreduction

Generally accepted indications for leukoreduction of blood products include (1) reduction of HLA alloimmunization risk in patients who require long-term platelet support, or for potential organ transplant recipients, (2) reduction of CMV transmission in at-risk patients, and (3) reduction of the rate of recurrent febrile nonhemolytic transfusion reactions.

At most centers, red blood cell components are filtered shortly after collection, eliminating leukocytes in a process called prestorage leukoreduction. Leukoreduced red blood cell components contain $<1.0 \times 10^6$ leukocytes/unit. Platelet components are filtered or undergo specific apheresis collection protocols that reduce the number of leukocytes. Leukoreduced platelet components contain $<5.0 \times 10^6$ leukocytes/unit. Generally accepted indications for leukoreduction of blood products include (1) reduction of HLA alloimmunization risk in patients who require long-term platelet support, or for potential organ transplant recipients; (2) reduction of cytomegalovirus (CMV) transmission in at-risk patients; and (3) reduction of the rate of recurrent febrile, nonhemolytic transfusion reactions. Controversial indications include (1) prevention of prion or viral reactivation; (2) prevention of postoperative infections; (3) reduction of tumor recurrence; (4) prevention of bacterial infection; (5) reduction in transfusion-related lung injury; and (6) reduction in transfusion-associated graft versus host disease.

A reduction of in-hospital mortality and serious nosocomial infections followed the adoption of leukoreduction of blood products in Canada. However, cost effectiveness of universal leukoreduction remains controversial. In addition to the financial burden, there is considerable loss of blood elements with filtration. Leukocyte-depleted RBC units deliver a statistically smaller total RBC mass than nonleukoreduced units. Despite the debate, in January 2001, the US Department of Health and Human Services (DHHS) Advisory Committee on Blood Safety and Availability (ACBSA) recommended universal leukoreduction of cellular blood products in the United States.

41.15 Irradiation

As noted previously, blood filtration decreases but does not eliminate white blood cell (WBC) contamination. When viable T-lymphocytes in any blood product are transfused into an immunosuppressed patient, they can proliferate and cause transfusion-associated graft-versus-host disease (TA-GVHD). TA-GVHD is characterized by skin, gastrointestinal, hepatic, and/or hematologic damage, occurring 10–28 days following a transfusion. It is associated with a high mortality. A radiation dose of 2500 Gy applied to cellular blood components will prevent donor T-lymphocytes from dividing and thereby prevent GVHD in the recipient. FFP and cryoprecipitate do not require irradiation as neither contains viable WBC and cannot cause TA-GVHD. Irradiation decreases RBC viability and causes potassium leakage, thus limiting storage duration to <28 days. For this reason, blood products are irradiated just prior to transfusion.

Indications for irradiated blood products include (1) mismatch of HLA haplotype between donor and recipient, (2) patients immunocompromised by chemotherapeutic regimens, (3) hematopoietic cell transplant patients, (4) neonates, and (5) patients with congenital cell-mediated immunodeficiencies.

Indications for irradiated blood products include (1) mismatch of HLA haplotype between donor and recipient; (2) patients immunocompromised by chemotherapeutic regimens; (3) hematopoietic cell transplant patients; (4) neonates; and (5) patients with congenital cell-mediated immunodeficiencies. At some institutions, patients receiving solid organ transplants also receive irradiated blood products. At our institution, all blood products are irradiated. The clinician must remember that irradiation does not eliminate viruses.

41.16 Washing

As mentioned above, RBC and platelet products contain small amounts of residual plasma proteins. These proteins may produce allergic or other reactions in the transfusion recipient. Pretransfusion washing of stored RBC and platelets eliminates proteins from the cellular blood product and is indicated for patients with (1) history of severe or recurrent allergic reactions associated with RBC transfusions; (2) IgA deficiency, when IgA-deficient blood is unavailable (host anti-IgA antibodies react with IgA in donor transfusion product); (3) red-cell T activation (in pediatrics, this is most commonly appreciated with necrotizing enterocolitis and invasive pneumococcal infections that cause the T antigen to be exposed on the RBC surface; anti-T antibodies in donor plasma may cause hemolysis); and (4) complement-dependent autoimmune hemolytic anemia (washing prevents the infusion of complement).

Standard blood cell processors utilized by blood banks "wash" cellular products traditionally with 0.9% sodium chloride (NS). Pretransfusion washing has been proven to decrease inflammation and immune mediation in adults with acute leukemia and children following cardiac surgery. However, washing is associated with RBC hemolysis and suboptimal platelet function. A recent publication of an *in vitro* study compared washing blood cells with NS versus Plasma-Lyte A. Plasma-Lyte A is an isotonic solution that is more physiologic with less acidity than NS. The authors found evidence of less hemolysis and improved platelet function in blood components washed with Plasma-Lyte A.

Our local washing protocol is for patients with documented IgA deficiency, history of severe allergic transfusion reaction, hematologic malignancies, intrauterine transfusions, newborns in the neonatal intensive care unit, neonatal alloimmune thrombocytopenic purpura, priming the extracorporeal membrane oxygenation circuit for infants younger than 1 year of age, neonates with positive circulating maternal isoagglutinin (anti-A/B) testing, patients expressing polyagglutination, liver transplant (two RBC units for initial cooler), pediatric cardiac surgery cases on cardiopulmonary bypass and 5 years old or younger (first RBC unit washed), and for intrauterine and neonatal exchange transfusions.

41.17 Transfusion-Related Immunomodulation

Allogeneic blood transfusions contain a myriad of immunomodulatory mediators that impact the recipient's immune function, termed transfusion-related immune modulation (TRIM). Transfusions contain large quantities of cellular and soluble antigens (alloantigens) and bioactive substances with proinflammatory and/or immunosuppressive properties. Following allogeneic blood transfusion, there is a decreased helper-to-suppressor T-lymphocyte ratio, decreased natural killer cell function, defective antigen presentation, and reduced cell-mediated immunity in the recipient. Transfused leukocytes likely contribute to these effects, and prestorage leukoreduction appears to temper but not eliminate TRIM.

Immunomodulation secondary to RBC transfusion was first suspected after an increase in renal allograft survival was noted after RBC transfusion. The suspicion was confirmed by performance of a prospective, randomized controlled study that illustrated an increase in allograft survival following RBC transfusion. The increased allograft survival following RBC transfusion raised the question whether TRIM might also increase cancer recurrence via downregulation of host immune surveillance targeting malignant cells, and increase

infectious complications. Meta-analysis of randomized controlled trials has not found increased cancer recurrence following transfusion but has demonstrated increased risk for nosocomial infections following transfusion and decreased health-care-associated infections in patients managed with a restrictive transfusion strategy.

Certainly the issue is complex. The immune response to critical illness is itself a dynamic process that is still poorly understood. The interplay between inflammation and the immune system in the critically ill is impacted by a multitude of patient-specific and treatment-specific factors that vary across time and context. The impact of the blood transfused is complicated by donor-specific factors as well as variations in the timing, number, volume, and type of product transfused; how the blood product is processed; and the duration of its storage. Future studies examining donor factors, blood processing, and storage methods/duration on the recipient's immune state is of great importance. Until our understanding of immune biology and critical illness expands, and TRIM can be mitigated entirely, adoption of blood conservation and restrictive transfusion strategies should be implemented.

41.18 Transfusion Reactions

Transfusion reactions can be classified as (1) hemolytic reactions, (2) febrile nonhemolytic reactions, (3) allergic or anaphylactic reactions, and (4) nonimmune transfusion reactions.

The United States blood supply is remarkably safe. However, incorrect blood product transfusion is still reported, involving approximately 1 in 500,000 components transfused, and can be associated with death or major morbidity. As of 2013, the overall incidence of transfusion-related complications reported to the American Association of Blood Banks (AABB) was 0.25% with the most common manifestations being fever (0.08%), allergic reactions (0.07%), and delayed serologic transfusion reactions (0.01%). In a more recent study, pediatric patients exhibited an overall higher adverse reaction rate (538 per 100,000 transfusions) compared with adults (278 per 100,000). Transfusion reactions can be classified as (1) acute or delayed hemolytic reactions, (2) febrile nonhemolytic reactions, (3) allergic or anaphylactic reactions, and (4) nonimmune transfusion reactions.

41.19 Hemolytic Reactions

Most hemolytic reactions result from ABO incompatibility, but acquired alloantibodies (anti-Rh or anti-Jka) can also cause hemolytic reactions. In hemolytic reactions, donor red blood cell antigens form complexes with recipient antibodies leading to cell death. ABO mismatch, usually due to clerical error, carries the most significant risk of morbidity and mortality from blood transfusions causing hemolysis and death in 8–44% of cases, depending on the volume of incompatible blood transfused. During hemolysis, cellular products are released that damage renal tubular cells and may lead to hemoglobinuria, acute tubular necrosis, and renal failure. The immunologic response generated by antigen-antibody complexes may trigger a systemic consumptive coagulopathy or DIC.

A severe hemolytic transfusion reaction manifests as fever, chills, rigors, hypotension, tachycardia, respiratory distress, hemoglobinuria, and/or bleeding. When a hemolytic transfusion reaction is suspected, the transfusion must be stopped immediately. Treatment involves volume support with isotonic fluids to prevent hypotension and to ensure urine output of 100 mL/h in the adult patient and 2 mL/kg/h in the pediatric patient. Inotropic support should be

considered in the setting of poor urinary output despite adequate volume resuscitation. Supportive care is necessary to prevent cardiopulmonary complications, and DIC should be treated appropriately.

Delayed hemolytic transfusion reactions (DHTR) by definition occur more than 24 hours after transfusion but have been reported as occurring from 3 to 30 days after transfusion. DHTR result from an anamnestic response to alloantibodies against minor RBC antigens that are undetectable at the time of transfusion and are most commonly reported in patients with sickle cell disease. Most patients present 1–2 weeks after transfusion with symptoms of hemolysis, including low-grade fever, jaundice, hemoglobinuria, and back pain. More severe episodes can result in hyperhemolysis, in which both autologous and allogeneic RBCs are destroyed. DHTR is likely underreported in sickle cell patients since the clinical presentation may be misidentified as a vasoocclusive crisis. Supportive care is usually adequate, but there are case reports suggesting the utility of steroids or IVIG in severe cases.

41.20 Febrile Nonhemolytic Reactions

Febrile nonhemolytic transfusion reactions (FNHTRs) occur in approximately 1 per 1200 transfusions. FNHTRs are defined as an increase in the temperature of at least 1°C during a transfusion in the absence of another cause. These reactions are generally mild and resolve spontaneously but can cause significant discomfort. FNHTRs may be characterized by fever, chills, and dyspnea occurring within 6 hour of the transfusion. These reactions are cytokine-mediated and are usually prevented with the use of leukocyte-reduced blood products. Since hemolytic reactions also may manifest as fever, management includes stopping the transfusion and evaluating for other possible transfusion reactions. FNHTRs often can be successfully treated with antipyretics, antihistamines, opioids, and/or clonidine (for rigors).

41.21 Allergic/Anaphylactic Reactions

Mild to moderate allergic reactions are common occurring in 1 per 1462 transfusions. The incidence of anaphylactic transfusion reactions is much less frequent with platelet components, reported in 1 per 34,000 transfusions, while FFP is responsible for the highest rates of reaction. Most allergic/anaphylactic transfusion reactions are presumed to be secondary to plasma proteins. Clinically, the reaction is similar to anaphylaxis from other causes and manifests as a rapid progression of hypotension, shock, angioedema, and respiratory distress. Management includes stopping the transfusion, the administration of subcutaneous or intramuscular epinephrine, airway management, oxygenation, and volume and inotropic/vasopressor support.

41.22 Other Transfusion Complications

Other transfusion reactions include volume overload, hypothermia, citrate toxicity, hyperkalemia, and transfusion-related acute lung injury (TRALI). Careful assessment and continued monitoring of the vascular volume status, pulmonary and renal functions, and electrolyte balance are necessary before and during infusion of blood products. The intensivist must be prepared to provide oxygen, ventilator support, and diuretics as necessary.

Neonates and infants are at greatest risk for volume overload and hypothermia from the transfusion of refrigerated blood. Standard practice is to transfuse 10–15 mL/kg of RBCs at a rate of 2–4 mL/kg/h. Slower rates of transfusion should be used in children in whom anemia is severe but which developed in an indolent nature. A classic example occurs in infants who are fed iron-poor cow's milk. The cow's milk causes occult intestinal blood loss that can lead to a slowly progressive and profound anemia with presenting hemoglobin values often less than 5 g/dL. Rapid transfusions may be appropriate for acute volume resuscitation, but lower transfusion volumes at slower rates of administration in stable infants are warranted. The risk of hypothermia increases when large volumes are transfused, especially through a central catheter. Hypothermia can be avoided by the use of a blood warmer.

Citrate, which binds to calcium, is an anticoagulant in RBC and plasma storage media. In large volume transfusions, citrate can lead to hypocalcemia. Citrate is metabolized in the liver to bicarbonate, and as a consequence, liver failure may increase the risk of citrate toxicity. In addition, simultaneously infusing calcium in tubing containing the blood product, or directly into the unit, may cause microemboli to form. The coadministration of lactated Ringer's solution with blood is also contraindicated due to its high calcium content.

Red cells lyse during prolonged storage, causing increased extracellular potassium to be present in the unit. It has been estimated that potassium levels may rise in the RBC unit by as much as 1 mEq/L/day during the first few weeks of storage. This potassium load is particularly dangerous to neonates and patients with renal insufficiency.

Pulmonary complications from blood transfusion comprise a spectrum of disease ranging in severity from mild pulmonary edema to TRALI. TRALI is defined as acute respiratory compromise with the onset of dyspnea, hypoxia, and noncardiogenic pulmonary edema within 6 hours of transfusion. All plasma-containing blood products (whole blood, RBC, platelets, FFP, cryoprecipitate, and IVIG) have the potential to cause TRALI, with an incidence of 1 in 62,640 transfusions. It has been postulated that TRALI results from an immunogenic response that leads to pulmonary capillary endothelial damage, capillary leak, and edema formation. It is thought that donor antibodies react with the antigens on the recipient WBCs resulting in complement activation. Granulocyte chemotaxin (C5a) attracts leukocytes to the pulmonary circulation and neutrophil lysosomal enzymes damage the capillary endothelium, resulting in capillary leak of fluid into pulmonary alveoli.

The diagnosis of TRALI is based on clinical criteria and is made primarily after excluding other possible conditions. Proposed clinical criteria for the diagnosis of TRALI include (1) the acute onset of pulmonary insufficiency (within 6 hours); (2) hypoxemia, specifically $PaO_2/FiO_2 < 300$ mm Hg; (3) bilateral fluffy infiltrates on chest radiography; (4) pulmonary artery wedge pressure $\leq$ 18 mm Hg; and (5) the absence of left atrial hypertension. Laboratory analysis of donor and recipient blood samples may further support the diagnosis.

If acute respiratory distress occurs during the transfusion, the transfusion should be stopped immediately. The treatment is primarily supportive; oxygenation and ventilation must be maintained and mechanical ventilation implemented as necessary. There is no supporting evidence for the use of corticosteroids or other antiinflammatory medications in the treatment of TRALI. TRALI typically resolves after 48–96 hours and does not cause permanent pulmonary damage. Although rare, this is a potentially severe complication of blood product transfusions.

Although TRALI should be considered in any pediatric patient with the onset of acute pulmonary disease within 6 hour following transfusion, the clinician should remember that other conditions may mimic TRALI. The diagnosis of acute intravascular volume overload (TACO: transfusion-associated circulatory overload) should be considered in any child with underlying cardiac insufficiency. Hemolytic transfusion reactions, or anaphylaxis due to the transfusion of IgA-containing products to a recipient with IgA deficiency, may also produce pulmonary manifestations. Several diagnoses, specific to the pediatric hematology-oncology population, may be confused with TRALI and include acute chest syndrome in transfused patients with sickle cell anemia, diffuse alveolar hemorrhage during bone marrow recovery in a hematopoietic cell transplant patient, and acute respiratory distress occurring during granulocyte transfusions.

41.23 Platelet-Specific Transfusion Reactions

Up to 20–30% of platelet transfusions are associated with transfusion reactions. Most of these are febrile nonhemolytic or allergic reactions. Since platelet units contain few RBCs, the incidence of hemolytic reactions following platelet transfusions is very low. Patients with a history of an allergic response following platelet transfusions are commonly premedicated with acetaminophen and/or diphenhydramine. The efficacy of this practice has not been demonstrated in the literature. Prestorage leukoreduction and platelet washing have been found to reduce the incidence of allergic reactions from platelet transfusions. With the advent of near-universal leukoreduction of blood products in the United States, the incidence of febrile nonhemolytic transfusion reactions has decreased, and allergic reactions are becoming the most common type of transfusion reactions.

Bacterial infections transmitted by platelet products can be divided into two categories: (1) those that arise from contamination of stored platelet products and, (2) those that occur from occult donor infections causing septic platelet transfusion reactions. Stored platelet products carry a high risk of bacterial contamination as they provide excellent growth media for bacteria while being stored at 20–24 °C for up to 5 days. Bacterial contamination occurs in 1 out of every 2000–3000 units of platelets. Transfusion-associated bacterial sepsis occurs in one-fourth to one-sixth of contaminated platelet transfusions. From 2009 to 2013, a fatality rate of 2.6 per year or 1.3 per million platelet transfusions was recorded by the US FDA in association with bacterial contamination. Currently, platelet products are routinely cultured in order to identify bacterial contamination and thereby reduce infection transmission. Attempts to eliminate bacterial contamination from platelet products include the use of ultraviolet light and psoralens. Both methods kill not only bacteria but also viruses and white blood cells.

Septic platelet transfusion reactions (SPTR) are attributed to the contamination of platelet units from donor skin flora or asymptomatic bacteremia in the donor. SPTR have an approximate incidence of 1 in 5000–15,000 transfusions and a mortality of 17.4%. There has been a decline in SPTR since the adoption of single donor platelet transfusions; SPTR occur five times more often in patients receiving platelet concentrates compared to those receiving single donor platelets. Increased donor exposure and the number of phlebotomies necessary to obtain pooled platelet concentrates likely contribute to the higher risk of bacterial contamination in pooled concentrates.

41.24 Infectious Risks

41.24.1 Identifying Risk

The development and implementation of molecular testing (PCR-based NAT) has greatly increased the sensitivity of infectious agent identification and has reduced the window period. However, the existence of this window period prevents complete identification of infected blood products by either serologic or molecular screening tests.

The AIDS epidemic of the late 1980s brought awareness and public concern regarding the spread of infectious diseases through transfused blood products. The American Red Cross responded by implementing more stringent donor history screening and improved donor testing. These approaches have dramatically reduced blood-product-related transmission of infectious diseases. The recent development and implementation of molecular testing (polymerase chain reaction (PCR)-based nucleic acid testing (NAT)) increased the sensitivity of infectious agent identification and has reduced the window period (the period of time during which a donor is potentially infectious but will have negative serological tests). However, the existence of this window period prevents complete identification of infected blood products by either serologic or molecular screening tests.

In the United States, donated blood is currently screened for *Babesia microti*, cytomegalovirus (some units), hepatitis B and C, HIV 1 and 2, human T-cell lymphotrophic virus (HTLV) I and II, *Treponema pallidum*, *Trypanosoma cruzi*, West Nile virus, and Zika virus.

41.25 Human Immunodeficiency Virus (HIV)

The American Red Cross tests all blood products for antibodies to HIV-1 and HIV-2 and for presence of HIV-1 RNA. By combined HIV antibody and minipool (6–1 specimens) nucleic acid testing (MP-NAT), the risk for HIV transmission following blood transfusion is currently cited at 1 in 1.5–2 million transfusions. This risk is not zero; and HIV transmission can still occur if (1) the donation is collected during the approximate 11 day window period when the donor is infected, but testing has not become positive; (2) HIV infection is with variant strains that cannot be detected by current assays; and/or (3) there is a clerical/testing error.

41.26 Hepatitis B and C

Routine screening for hepatitis B virus (HBV) with MP-NAT testing has been implemented in the United States. This practice has decreased the risk of transfusion-transmitted HBV to 1 in 1.1 million. PCR-based NAT testing for hepatitis C virus (HCV) was implemented in 1990. This approach has reduced the HCV window period to approximately 3 days and has decreased the transfusion-transmitted risk of HCV to 1 in 1–2 million units. Hepatitis A and E do not have chronic phases; the viruses are transmitted during the acute viremic phase and should be identified on donor screening. Therefore, specific serologic or molecular screening assays are not used.

41.27 Cytomegalovirus

Cytomegalovirus (CMV), a herpes virus, is transmitted by leukocytes and, therefore, is associated only with *cellular* blood product transfusions. Any immunosuppressed patient is at risk of acquiring transfusion-related systemic CMV infection, and CMV is a significant cause of mortality in the hematopoi-

etic cell transplant patient. These patients must receive CMV seronegative blood to avoid CMV transmission. Unlike testing for HIV and Hepatitis, not all blood is screened for CMV. CMV antibody testing is performed on select units to maintain a local CMV-negative supply to meet local patient demands. As antibody testing for CMV is not specific, and 30–70% of donors (region-specific variations exist) test positive for CMV antibodies, additional blood processing measures have been adopted for high-risk patients in order to prevent transfusion-transmitted CMV. Filtered, leukoreduced blood components are an acceptable alternative if CMV-negative blood is not available.

41.28 West Nile Virus

A seasonal flavivirus, the West Nile virus is a single-stranded RNA virus with high viral activity during the warmer months. Transmission is predominantly between mosquitos and birds although it can infect humans. Eighty percent of those infected are asymptomatic with the remainder having febrile illnesses and gastrointestinal symptoms. However, <1% will develop neuroinvasive disease that can lead to irreversible neurologic damage, coma, and death. Transfusion transmission occurs only from acutely infected asymptomatic persons (opposed to chronically infected donors). For this reason, only PCR MP-NAT is utilized and serologic screening is not performed. In total, 4156 cases including 284 deaths were reported in the United States in 2002, leading to implementation of PCR NAT for the West Nile virus in 2003. Despite MP-NAT testing, breakthrough transmission occurred, leading to more recent adoption of a targeted individual donation (ID) testing strategy. This targeted strategy involves real time MP-NAT tracking over specific geographic regions with a predetermined trigger to convert to utilization of ID-NAT testing on all units. Typically, the detection of a MP-NAT positive donation triggers utilization of ID-NAT testing of all units. Local regions have their own specific criteria for returning to MP-NAT testing. From 2003 to 2017, only 12 cases of transfusion-transmitted West Nile virus were identified.

41.29 Adult T-Cell Lymphoma/Leukemia

Adult T-cell lymphoma/leukemia (ATLL) is a peripheral T-cell neoplasm associated with infection by human T-lymphotrophic virus (HTLV), type I and II. These patients are primarily adults with antibodies to HTLV-I. The virus is endemic in the islands in southern Japan, the Caribbean basin (Jamaica), Trinidad, Africa, and in the southeastern portion of the United States. The virus may be transmitted through sexual contact, breast milk, or through blood products. Antibody screening for HTLV I/II is confirmed with a 2016 FDA-licensed confirmatory assay. Transfusion-transmitted HTLV-I/II is estimated to occur in 1 in 2.7 million units.

41.30 Zika Virus

Like West Nile virus, Zika virus is a mosquito-borne flavivirus. Most infected persons are asymptomatic or have mild flu-like symptoms. However, the unborn children of pregnant women who become infected have higher incidence of microcephaly, neurodevelopmental disability, and fetal demise. Zika virus causes placental infection and injury/insufficiency that may cause fetal death.

As a neurotropic virus, infection of the fetal brain causes abnormal neuronal development including vision and hearing loss, hyper/hypotonia, irritability, and seizures. Minipool testing was adopted in the United States in 2018, with transition to ID-NAT in similar fashion as that described for West Nile virus. Transfusion transmission was estimated to be 1 in 480,654 units during 2016–2017 in the United States where only 9 were positive for the Zika virus.

41.31 Other Viruses

Many other infectious agents have the potential to be transmitted through blood product transfusions. The availability of specific serologic and molecular tests for many agents is lacking, and in such circumstances, positive donor history leading to deferment is relied upon to prevent transmission.

Severe acute respiratory syndrome (SARS) is a viral respiratory disease first identified in the Guangdong province of China in November 2002 as the result of a mutated coronavirus. Most infected persons have febrile flu-like symptoms. The outbreak spread to 37 countries and had a mortality rate of 9.6% according to the World Health Organization. The average incubation period is 4–6 days; there is no cure or vaccine. No cases have been reported worldwide since 2004. In 2017, pathogenesis was identified from cave-dwelling horseshoe bats. It is unknown whether SARS can be transmitted through transfusions. The FDA has published recommendations on donor suitability for the prevention of transfusion-transmitted SARS. Donors are deferred for 21 days after any possible exposure or travel to a SARS-affected community, 21 days after exposure to someone suspected to have SARS, and 3 months after recovery from suspected SARS.

Parvovirus B19 is potentially transmissible through blood product transfusions. Parvovirus B19-associated illness is rarely clinically significant except in pregnant women (where it can cause hydrops fetalis), in those with hemolytic anemia (where it can cause aplastic crisis), and in immunocompromised persons. It is estimated that parvovirus B19 viremia is present in approximately 0.025% of donors, yet there have only been rare reports of its transmission in plasma-derived blood products. A 2009 study using a linked donor-recipient repository and a sensitive quantitative B19V DNA PCR assay found no transfusion-transmission to susceptible recipients with concentrations $<10^6$ IU/mL. These results support the belief that no specific donor testing for parvovirus B19 is necessary. Nanofiltration and/or heat inactivation of plasma products is currently utilized to prevent transmission.

The spirochete *Treponema pallidum* causes syphilis and can be transmitted through sexual contact and blood transfusions. No cases of transfusion-transmitted syphilis have been reported since 1968 due to the success of serologic screening of donors using automated treponemal-based testing which continues to be mandatory in the United States and is recommended for all donors worldwide by the World Health Organization.

Malaria can also be transmitted through the blood stream. The Center for Disease Control estimates that there is one case of transfusion-transmitted malaria every 2 years in the United States. In the United States, there is no FDA-approved serologic test to screen blood donors for malaria. The prevention of transfusion-transmitted malaria has been accomplished by donor deferral based on travel history: 1 year for travelers to endemic areas if they have no symptoms, and 3 years for immigrants or visitors from malarious countries if they are asymptomatic, or 3 years from their most recent visit for former residents of malarious areas who are now US citizens and have returned

from a visit. Those with history of malaria are deferred for 3 years from the time they became asymptomatic.

An outbreak of variant Creutzfeldt-Jacob disease (vCJD), a prion linked to bovine spongiform encephalopathy, occurred in the United Kingdom in 1996 raising the concern for vCJD transfusion transmission. Since 2002, the US FDA has adopted a policy for deferred donation for donors who have spent >3 months in the United Kingdom between 1980 and 1996, or have spent >6 months in Northern Europe during this time period, have lived >5 years total in Europe, or have received a blood transfusion while in the United Kingdom.

Concern over bioterrorism has raised questions as to whether orthopoxviruses (smallpox, vaccinia, monkeypox) can be transmitted through blood transfusions. The success of the vaccination campaign to eradicate the disease led to the last natural case of smallpox in the early 1970s in the United States and 1977 in Somalia. As naturally occurring cases became less frequent than vaccine-induced cases, routine vaccination was discontinued in the United States in 1972. In 1986 routine vaccination ceased worldwide, though vaccination for laboratory workers at risk for exposure remains indicated. Antiviral treatments have been developed, and in July 2018, the FDA approved ticovirimat for the treatment of smallpox.

41.32 Transfusions in Special Patient Populations

41.32.1 Neonates

RBC transfusion practices vary greatly in neonatal and pediatric intensive care units across the United States. Evidence-based transfusion guidelines do not exist and expert opinion has primarily driven transfusion practices. However, it is established that high numbers of neonates are transfused. Anemia may result from bleeding, hemolysis, or congenital aplasia. Physiologic anemia with an inadequate bone marrow response, low levels of erythropoietin, poor nutritional status, iron deficiency, shorter RBC life span, and frequent blood sampling contribute to anemia. Blood group incompatibility, hemoglobinopathies, and/or sepsis, if present, may compound the anemia. In hemodynamically stable nonbleeding newborns, transfusions are often given for a variety of clinical conditions that have been associated with anemia and that are difficult to quantify such as lethargy, poor growth, apnea, and oxygen requirement. In addition to the "standard" risks of blood transfusions, premature infants have greater risk for iron and volume overload, and retinopathy of prematurity (ROP) and necrotizing enterocolitis (NEC) from oxidant injury.

A 2011 Cochrane review of four low- versus high-transfusion trials in the very-low-birth-weight neonate found no difference between the groups in mortality or complications such as ROP, bronchopulmonary dysplasia, or neurologic outcomes. The "low" transfusion threshold was 10, 8.5, and 7.5 g/dL for neonates without respiratory support and 11.5, 10, and 8.5 for those with respiratory support at 1, 2, and 3 weeks of life, respectively. Meta-analyses in 2014 and 2015 followed, supporting the Cochrane review's findings; fewer transfusions and donor exposures in restrictively managed subjects exhibited equivalent morbidity and mortality to liberally managed subjects. Furthermore, fewer infections were identified in the restrictive groups. The British Committee for Standards in Hematology 2016 presented their recommendations for restrictive transfusion practices in very preterm babies which are illustrated in Table 41.3. The caveat to these guidelines is that many stable, growing pre-

Table 41.3 Suggested transfusion thresholds for very preterm (<32 weeks gestation) neonates (New et al. 2016)

Postnatal age	Suggested transfusion threshold hemoglobin (g/dL)		
	Ventilated	On oxygen or noninvasive ventilation	Off oxygen
First 24 hours	<12	<12	<10
≤ Week 1 (day 1–7)	<12	<10	<10
Week 2 (day 8–14)	<10	<9.5	<7.5[a]
≥ Week 3 (day 15 onward)	<10	<8.5	<7.5[a]

[a] 8.5 g/dL depending on clinical situation

mature babies who do not require oxygen tolerate Hb levels of 6.5–7.0 g/dL when their iron level is maintained and they have an adequate reticulocytosis.

A multicenter Transfusion of Premature (TOP) trial randomized infants ≤1000 g birth weight and <29 weeks gestational age to receive RBC transfusions to a restrictive versus liberal transfusion protocol. TOP is powered to demonstrate which strategy reduces the primary outcome of death or neurodisability in survivors at 22–26 months. This study is ongoing and hopefully will provide additional data in this low-birth-weight group. Secondary studies examining the effect of blood transfusion on cerebral and somatic oximetry (NIRS study) will determine differences in cerebral oxygenation and fractional tissue oxygen extraction between transfusion groups during red blood cell transfusions. Currently, there are no evidence-based transfusion thresholds for older and term neonates. Despite this, we recommend a judicious transfusion approach to the neonate, with every effort to follow blood conservation practices.

Use of "pedipacks", multiple small volume packs from a single dedicated RBC unit for the life span of that unit should be utilized, acknowledging that this may increase the storage duration of the cells transfused. Blood should be prestorage leukoreduced and irradiated within 14 days of collection for preterm and immunodeficient neonates to avoid transfusion-associated graft-versus-host disease. Every effort to minimize phlebotomy losses should be undertaken, including delayed cord clamping and utilization of cord blood for initial sampling.

Red blood cell preservatives (mannitol, glucose, sodium chloride, phosphate, adenine) are manipulated in order to lengthen the unit's storage duration to 42 days. As previously described, prolonged storage can increase potassium, adenine, and mannitol contents. A solute load of such magnitude may lead to an osmotic diuresis, altered cerebral microcirculation, and renal toxicity in the small infant. Therefore, alternative RBC preservatives have been developed for use in neonates. AS-1 (750 mg/100 mL mannitol and 27 mg/100 mL adenine) and AS-3, (30 mg per 100 mL of adenine, but no mannitol) are safe for small volume (5–15 mL/kg) transfusions in neonates.

41.33 Congenital Heart Disease

Children with congenital heart disease (CHD) have historically been heavily transfused to maintain high Hb levels pre- and postpalliative or reparative surgical procedures. Those with congenital cardiac disease often have associated chromosomal abnormalities including chromosome 22q deletion of velocar-

diofacial syndrome, and thus, may be at increased risk of T-lymphocyte deficits. Consequently, it is our standard practice to transfuse this population with filtered and irradiated blood products. Two pRBC units are prepared by our blood bank for all congenital cardiac pediatric patients requiring cardiopulmonary bypass. One unit, a "fresh" pRBC unit (<5 days old) that is poststorage washed, is used first to prime the bypass circuit, with the residual volume available for additional transfusion as required. FFP is not given routinely on cardiopulmonary bypass nor used in the pump prime. The second pRBC unit is irradiated and leukoreduced, and patients are maintained on a filtered and irradiated protocol for the remainder of their hospitalization until their genetic profile is known.

During cardiopulmonary bypass, the balance between bleeding and thrombosis is deranged. Thrombocytopenia results from platelet consumption and hemodilution. In addition, platelets are rendered dysfunctional secondary to hypothermia and following their activation and release of mediators. The process of traversing the bypass circuit promotes thrombosis; so heparin and fibrinolytic agents are used intraoperatively and levels are monitored with activated clotting times (ACT). There is also a concomitant risk of bleeding secondary to hemodilution of coagulant proteins and a cytokine-driven inflammatory response to the bypass circuit. Individual physiology, the degree of cyanosis, and postoperative hemodynamic instability may further contribute to the coagulopathy experienced by these children. Thrombosis of surgical grafts, artificial valves, and conduits are often incompatible with life. Therefore, infusions of procoagulant blood products should be used only after careful considerations of the associated risks and benefits.

Concern that children with CHD, and/or cyanosis, cannot raise their cardiac output to maintain oxygen delivery in response to anemia and/or bleeding perioperatively has driven transfusion practice to maintain very high Hb levels (typically >12 g/dL) in this population. A 2010 subgroup analysis of 125 children in the TRIPICU study with CHD following cardiac surgery was the first prospective study to include subjects with CHD. These authors found no significant difference in new or progressive multiorgan dysfunction (primary outcome), ICU length of stay, or mortality in those treated with a restrictive (<7.0 g/dL) versus a liberal (<9.5 g/dL) transfusion strategy. Neonates and children with single ventricle physiology and mixing cardiac lesions causing cyanosis were excluded from this analysis, and subjects could be enrolled up to 7 days from time of PICU admission.

In 2013, de Gast Bakker and colleagues performed a single center, prospective, randomized trial in 107 acyanotic (oxygen saturation > 95%) children aged 6 weeks to 6 years comparing outcomes between those managed with RBC transfusion for Hb <8.0 g/dL versus 10.8 g/dL from anesthesia induction to hospital discharge. The restrictive group received significantly lower RBC volume, shorter hospital length of stay, and lower hospital costs with similar adverse events.

In 2017, Cholette performed a prospective, randomized controlled conservative versus liberal transfusion trial in 162 infants ≤10 kg presenting for cardiac surgery (palliative or complete repair). Conservative subjects were transfused for Hb < 7.0 g/dL for biventricular repairs or <9.0 g/dL for palliative procedures plus a clinical indication. Liberal group subjects were transfused for Hb <9.5 g/dL for biventricular repairs or <12 g/dL for palliative procedures regardless of the clinical situation. One hundred and five infants having complete reparative procedures were managed with 100% compliance in the restrictive arm. The primary aim of the study was to assess the safety of the conservative transfusion strategy and compare transfusion rates and mea-

sures of oxygen utilization between groups. The study is noteworthy in that the intervention began at the time of direct admission to the pediatric cardiac intensive care unit (PCICU) from the operating room, and there were no exclusions for bleeding or hemodynamic instability. The daily Hb concentration was significantly lower in the conservative group, and the percentage of patients requiring a RBC transfusion and number and volume of RBC transfusions were all significantly lower in the conservative group. Despite lower Hb concentrations within the conservative group, lactate, arteriovenous oxygen difference (avO_2diff), and clinical outcomes were similar between groups.

Taken as a whole, these three trials appear to support the contention that children with CHD undergoing biventricular repairs tolerate conservative transfusion practices and lower Hb levels, even in the immediate postoperative period. The cardiac TAXI subgroup consensus reflects the evidence and recommends that children undergoing biventricular repairs who are hemodynamically stable and have adequate oxygenation and end organ function not be transfused if their Hb is ≥7 g/dL.

As described above, children with complex CHD and/or intracardiac or great vessel level shunting resulting in cyanosis are particularly vulnerable and may be more dependent on higher Hb levels to maintain oxygen delivery if they cannot augment their cardiac output or increase their oxygen saturation. Additionally, these children undergo more complex and lengthy surgical palliative repairs (that may also include deep hypothermic circulatory arrest), are more susceptible to bleeding/coagulopathy/SIRS from cardiopulmonary bypass, and have a much higher perioperative morbidity and mortality. In a small, single-center, prospective, randomized controlled trial, Cholette compared a restrictive (<9.0 g/dL) vs. liberal (≥13 g/dL) RBC transfusion strategy in 60 infants and children with single ventricle physiology undergoing palliative cavopulmonary connection (bi-directional Glenn and Fontan procedures). Children managed with a restrictive transfusion strategy (Hb <9.0 g/dL) received significantly fewer transfusions and appeared to tolerate the lower Hb levels with no difference in oxygen utilization or clinical outcomes compared to those maintained at higher Hb (≥13 g/dL) levels. Results of this work primarily informed the TAXI cardiac subgroup consensus recommendation that transfusion be avoided in those children with single ventricle physiology who are undergoing stage 2 and 3 procedures if their Hb level is >9.0 g/dL.

The 2017 Cholette transfusion trial (described above) included 57 infants undergoing palliative procedures (including 12 Norwood procedures; 6 per group) with the intervention starting immediately upon postoperative PCICU admission. Subjects were followed until the time of death, a decision to cannulate for ECMO, floor transfer, or postoperative day #28. There was 79.3% compliance in the conservative group, and in the six instances where transfusions were given above the Hb threshold (<9.0 g/dL with clinical indications), five were for clinical indications and one at CT surgeon's request prior to chest closure. The conservative group had similar outcomes to liberally managed subjects. Although this study is not without limitations, it does provide initial data supporting the ideology that transfusions should be reserved for clinical indications, and that transfusion to Hb "trigger" should be avoided even in this particularly tenuous patient population. Additionally, this work provides support for the bedside clinician's judgment to hold transfusion despite a low Hb level when compelling clinical indication for a transfusion does not exist. Informed by this work, the TAXI cardiac subgroup recommended to avoid RBC transfusions in children undergoing stage 1 procedures with Hb >9.0 g/dL if the patient has stable hemodynamics, adequate oxygenation (for their

cardiac lesion), and end organ function. Further work is needed to confirm these results. It would appear that each contributor to oxygen delivery should be optimized before RBC transfusion is administered to children with CHD.

41.34 Extracorporeal Membrane Oxygenation (ECMO)

Much like cardiopulmonary bypass, maintaining a balance between hemorrhagic complications and circuit thrombosis remains a challenge while providing ECMO support. Patients on ECMO are typically maintained on a heparin infusion to prevent clotting of the circuit, and various center-specific measures of anticoagulation are followed (i.e., anti-Factor Xa levels, aPTT, PT, and platelet count). Additionally, activated clotting time (ACT) is typically followed as a bedside point of care test of global clot generation, with a goal between 180 and 220 seconds with higher target levels for lower ECMO flows.

ECMO is a tool utilized for many clinical indications, including but not limited to refractory hypoxia/respiratory failure, myocardial failure, sepsis, and postoperative cardiac surgery. The bedside clinician must determine whether the goal is for anticoagulation of the ECMO circuit alone to maintain its flow or to treat patient thrombosis. Unfortunately, neonates and children managed on ECMO frequently have significant bleeding complications and commonly receive multiple RBC transfusions each day. Bleeding can be the result of the underlying disease state that led to cannulation for ECMO and can also be exacerbated by ECMO and the anticoagulation it requires. Utilization of ECMO may also incite a consumptive and dilutional coagulopathy, thrombocytopenia, and platelet dysfunction, which can lead to significant hemorrhage and require large numbers of RBC and plasma transfusions. In addition to bleeding around invasive lines/catheters, intracranial hemorrhage can occur (particularly in neonates) despite meticulous care and can be devastating. As ECMO often utilizes large numbers of RBCs, FFP, and platelet units, there must also be careful attention to, and correction of, electrolyte imbalances that may arise following large volume transfusions (hypocalcemia, hyperkalemia). It is our protocol to wash the priming RBC unit given on ECMO to prevent hyperkalemia secondary to large volume RBC transfusion.

The extracorporeal life support organization (ELSO), a national registry of patients supported on ECMO, tracks bleeding but not transfusion data. ELSO guidelines currently recommend maintaining a hematocrit >40% to maintain oxygen delivery at the lowest tolerable ECMO flow rate. However, studies have found that there is no benefit in keeping the hematocrit >35% for patient's on ECMO, and despite these guidelines, ECMO directors report lower RBC transfusion thresholds in their practice. In a survey conducted by Bembea in 2014, the median hematocrit prompting RBC transfusion was 35% with a range of 25–40%. Platelet and coagulant product transfusions are guided by center-specific protocols, adjusted for the ECMO indication, and the presence or absence of bleeding. It has been demonstrated from observational studies that larger numbers of transfusions are associated with worse clinical outcomes and there is interest across pediatric intensivists in discerning the optimal Hb thresholds for patients supported in such a manner. There are no data currently to support recommendations on transfusion thresholds in patients supported on ECMO. However, as with other patients, we believe that transfusions should be judicious and based primarily on clinical indications such as evidence of inadequate cardiorespiratory support or end organ compromise.

41.35 Uremic Patients

The association between renal disease and bleeding is well recognized. Renal failure is often complicated by mucocutaneous bleeding secondary to impaired hemostasis. The use of hemodialysis or peritoneal dialysis has greatly decreased the occurrence of hemorrhagic complications, but clinicians must remain aware of the hemorrhagic tendency of the uremic patient. The hemostatic defect associated with renal failure is multifactorial. Alterations in platelet metabolism, vascular and smooth muscle endothelial cells, and abnormal interactions between platelets and the vessel wall have been found in the uremic patient. The management of bleeding in the uremic patient includes increasing von Willebrand factor (vWF) to improve platelet dysfunction. The use of cryoprecipitate for this indication has been replaced by intravenous DDAVP which stimulates the release of Factor VIII and vWF from endothelial cells. Regarding the use of pRBCs, current practice is to adjust dialysis and transfuse patients with renal failure to maintain a hematocrit above 30%. Recombinant human erythropoietin therapy is standard treatment for anemia of renal insufficiency, and its use generally decreases the number of RBC transfusions.

As described previously, the concentration of extracellular potassium increases as RBC storage duration increases. Renal failure patients requiring RBC transfusions should receive blood less than 5 days "old" to prevent hyperkalemia. If such blood is unavailable, "older" blood can be washed immediately prior to transfusion to reduce its potassium content.

41.36 Patients with Inherited Bleeding Disorders

Patients with classic hemophilia (hemophilia A) have insufficient Factor VIII levels. Factor VIII (FVIII) concentrate is, therefore, the preferred replacement modality in these patients. Indications for FVIII infusions in children with this form of hemophilia include preparation for an invasive or surgical procedure, bleeding, or prophylaxis to prevent further joint disease. Children with severe hemophilia often receive routine infusions for the primary or secondary prevention of bleeding episodes. The Medical and Scientific Advisory Council of the National Hemophilia Foundation recommends recombinant FVIII as the first-line treatment of these patients. There are now several FDA-approved recombinant FVIII products with longer half-lives. Plasma-derived virally inactivated FVIII concentrates are also available. Patients with hemophilia B (Christmas disease) have insufficient Factor IX levels (FIX), and FIX is the preferred replacement for these patients. There are three types of FIX available: recombinant FIX (which is preferred), plasma-derived FIX, and prothrombin complex concentrates. Each can be used for the treatment of acute bleeding or for prophylaxis. Recombinant FIX products with longer half-lives are also available. The selection of the most appropriate product is complex, individualized, and subject to refinement by the primary hematologist. However, if there is severe bleeding or if specific factor replacement is unavailable, FFP should be given.

Von Willebrand disease (VWD) is the most common inherited bleeding disorder in the United States. Patients typically experience mucocutaneous bleeding of variable severity. Type 1 patients express a partial deficiency of von Willebrand factor, which can sometimes be alleviated by DDAVP during hemostatic challenges. Individuals with type 2 VWD express a dysfunctional protein and may require human-plasma-derived vWF, which is derived from

pooled human plasma. Type 3 patients exhibit complete deficiency of vWF and may experience bleeding severity equivalent to that of hemophilia patients. They also require human-plasma-derived vWF perioperatively or after trauma.

41.37 Oncology/Transplant Patients

Anemia is quite common in patients with malignancies. Its origins are multifactorial: (1) ineffective or suppressed erythropoiesis secondary to chronic disease, marrow infiltration, or myelosuppressive therapy; (2) peripheral destruction from alloimmune and/or autoimmune hemolysis; and (3) hemorrhage secondary to acquired coagulopathies and thrombocytopenia, anatomic lesions, or surgical procedures. Transfusion therapy for these patients is complicated by persistent cytopenias and immunosuppression, but as for other groups, the use of hematopoietic growth factors has decreased the need for transfusions.

At our institution, patients with malignancies are placed on a blood bank protocol consisting of irradiated, filtered, and leukoreduced blood products. At some institutions, CMV-negative blood products are utilized until the CMV serostatus of the individual is known. Hematopoietic cell transplant (HCT) patients receiving myeloablative therapy are particularly susceptible to bleeding complications. Both HCT and solid organ transplant recipients are immunosuppressed and at risk for persistent cytopenias, infections, and transfusion-associated infectious and immunologic complications. Immunosuppressed oncology and transplant patients are at risk for developing TA-GVHD as described previously.

One unit of PRBC contains approximately 250 mg of iron. Patients requiring multiple red cell transfusions, such as patients undergoing myelosuppressive chemotherapy or patients with aplastic anemia or thalassemia major, are at risk for developing iron overload. Clinically significant iron overload in children develops after the receipt of about 10 units. There is no physiologic way for the body to excrete excess iron. After plasma transferrin is saturated, excess iron binds to other plasma proteins and molecules, which are then taken up by the parenchymal cells of the liver, heart, and endocrine organs. Excess iron interacts with hydrogen peroxide, yielding reactive oxygen species, which cause tissue injury, inflammation, and fibrosis. Measurement of ferritin is the least invasive screening tool for iron overload, but it should be interpreted with caution in the setting of inflammation since ferritin is an acute phase reactant. T2* MRI has supplanted liver biopsy for corroborative measurement of liver iron content. Iron overload may be addressed by phlebotomy in patients without anemia or treated with chelation in patients with concurrent anemia.

41.38 Sickle Cell Disease

Predominantly affecting black and Hispanic Americans, sickle cell disease results from a single point mutation in the beta-globin gene. The resulting hemoglobin molecule undergoes abnormal polymerization in the setting of deoxygenation. The erythrocyte reversibly then irreversibly deforms into a crescent or "sickle" shape, which poorly traverses the microvasculature. Vasoocclusion is central to the pathophysiology of the disease, but research has demonstrated that chronic inflammation, hypercoagulability, and nitric oxide deficiency contribute to the widespread organ damage that characterizes sickle cell disease.

RBC transfusions play a critical role in the acute and chronic management of sickle cell complications. Simple transfusions are indicated for moderate acute chest syndrome, moderate to severe splenic sequestration, and symptomatic anemia. Exchange transfusions are necessary for the acute management of stroke, severe acute chest syndrome, severe sickle hepatopathy, and multiorgan failure syndrome. Simple or exchange transfusions may be used preoperatively to reduce the risk of postanesthesia acute chest syndrome, depending on the patient's baseline Hb. In general, the Hb should not be elevated above 10 g/dl in sickle cell patients as this can lead to hyperviscosity and organ dysfunction. Chronic transfusions are effective as secondary prophylaxis after stroke as well as primary prophylaxis in patients identified by transcranial Doppler as being at higher risk for stroke.

After approximately 10 units, patients should be evaluated and treated for transfusion-related iron overload. Chronic and multiple intermittent transfusions also increase the likelihood of alloimmunization in these patients; it has been reported in 12% of children and up to 27% of adults. Alloimmunization may cause delayed hemolytic transfusion reactions and delays in obtaining compatible units. Blood banks may minimize the development of alloimmunization by employing extended RBC phenotyping for, at a minimum, C, E, and K antigens.

41.39 Alternative Therapy

41.39.1 Erythropoietin

In critically ill patients, endogenous erythropoietin levels are commonly low despite the presence of anemia. However, research has demonstrated that the bone marrow of the ICU patient is extremely responsive to exogenous erythropoietin. Consequently, it has long been postulated that administering exogenous erythropoietin to these patients would reduce anemia and the necessity of transfusion support. The main drawbacks to using erythropoietin therapy in the critically ill patient is the length of time between administration and the resultant marrow response (weeks), and the heightened risk for thrombosis. Small studies have demonstrated increased reticulocytosis with erythropoietin administration, but no increase in final Hb concentration or reduction in transfusion number. A prospective, randomized controlled trial of 1460 critically ill adults demonstrated no difference in transfusion requirements in epoetin alpha-treated subjects. General consensus is that widespread use of erythropoietin would have little impact on the transfusion requirements of children admitted to the PICU. It is difficult to determine prospectively which PICU patients will have an extended length of stay, will require multiple RBC transfusions, and would therefore benefit from erythropoietin therapy. That said, the use of erythropoietin as a blood conservation therapy for patients with chronic anemia, i.e., secondary to chronic renal failure, cancer etc., is well supported.

41.40 Hemostatic and Other Agents and Blood Substitutes

A variety of agents are now available to decrease bleeding, promote hemostasis, and decrease the number of required blood product transfusions. Agents used to increase concentrations of clotting factors include DDAVP, estrogens, and vitamin K. Agents to increase platelet concentrations and activity include

recombinant thrombopoietin and recombinant human interleukin-11. Antifibrinolytic agents include tranexamic acid and aminocaproic acid. Topical agents such as hemostatic sealants and dressings are also available. Review of the mechanisms of action and clinical indications for these agents is beyond the scope of this chapter. However, the intensivist should be aware that these agents exist, and that they may be of great benefit to patients in certain situations.

In addition to the development of volume expanders (that restore volume, but do not carry oxygen), oxygen-carrying blood substitutes are being developed as a blood substitute for individuals whose religious beliefs oppose blood product transfusions (i.e., Jehovah's Witnesses), where appropriately matched products are unavailable, to eliminate possible transfusion-transmitted diseases, to combat chronic blood shortages, and/or to provide product where refrigeration is not available. These include hemoglobin-based oxygen carriers (HBOC) and perfluorocarbon-based oxygen carriers (PFBOC). There are case reports citing limited success with oxygen-carrying blood substitutes, but these products are not currently available for use in the United States.

41.41 Summary

Understanding the role of blood products in the management of critically ill patients is extremely important. Blood product transfusions are exceedingly common and likely to increase as medical advances in the care of critically ill patients continue. The decision to administer a blood product must be based on a clear understanding of the benefits and risks of the transfusion and made in the context of the clinical condition of the patient. It is of paramount importance that the clinician is familiar with the types of blood products available, their composition, the indications for their use, and the associated potential risks. Blood conservation strategies and restrictive transfusion practices should be implemented whenever possible.

Review Questions

1. A 4-year-old male with multiple trauma develops symptomatic anemia. Prior to administering a packed red blood cell transfusion, the child's parents ask about the risk of HIV transmission. You answer that the risk is:
   A. <1 in 10,000
   B. <1 in 100,000
   C. <1 in 1 million
   D. <1 in 1.5–2 million
   E. <1 in 4 million

2. Transfusion-related acute lung injury (TRALI) is best defined as:
   A. Acute onset of chest pain within 1 hour of transfusion, hypoxemia, (PaO_2/FiO_2 < 300 mm Hg), bilateral infiltrates on chest radiography, and absence of left heart failure
   B. Acute onset of chest pain within 6 hour of transfusion, hypoxemia, (PaO_2/FiO_2 < 300 mm Hg), bilateral infiltrates on chest radiography, and absence of left heart failure
   C. Acute onset of pulmonary insufficiency within 1 hour of transfusion, hypoxemia, (PaO_2/FiO_2 < 300 mm Hg), bilateral infiltrates on chest radiography, and absence of left heart failure

D. Acute onset of pulmonary insufficiency within 6 hour of transfusion, hypoxemia, (PaO_2/FiO_2 < 300 mm Hg), bilateral infiltrates on chest radiography, and absence of left heart failure
E. Acute onset of pulmonary insufficiency within 6 hour of transfusion, hypoxemia, (PaO_2/FiO_2 < 300 mm Hg), hypercarbia ($PaCO_2$ >50 mm Hg), bilateral infiltrates on chest radiography, and absence of left heart failure

3. The most correct statement regarding anemia and red blood cell transfusion in the PICU is:
   A. Red blood cell transfusion should be considered after other measures to improve oxygen delivery and optimize hemodynamics have been exhausted.
   B. Maintaining hemoglobin levels >8.0 g/dL in critically ill children is an appropriate therapeutic target as it reduces ICU morbidity and mortality.
   C. Oxygen delivery by transfused red blood cells is comparable to that of native red blood cells and consistently increases tissue oxygen availability.
   D. Red blood cells are produced by the removal of plasma and all cellular components other than red blood cells.
   E. The ability of the heart to increase cardiac output in response to severe anemia is compromised in children with underlying congenital heart disease, and they should be maintained with hemoglobin levels >10 g/dL.

4. Storage techniques that lengthen RBC lifespan may result in detrimental physiologic changes that include:
   A. Depletion of 2,3-diphosphoglycerate (2,3-DPG) with resultant decreased oxygen affinity and increased off-loading of oxygen to the tissues
   B. Increase in 2,3-diphosphoglycerate (2,3-DPG) with resultant decreased oxygen affinity and decreased off-loading of oxygen to the tissues
   C. Increase in endogenous antioxidants resulting in damage to cytoskeletal proteins and membrane phospholipids
   D. Morphological changes including the loss of the normal biconcave disc shape ultimately leading to schistocyte formation
   E. Morphological changes including the loss of the normal biconcave disc shape ultimately leading to spherocyte formation

5. A 10-year-old girl with acute lymphocytic leukemia is in the PICU recovering from sepsis. She is extubated and off hemodynamic support. Her most current cell counts are white blood cell count 3500/μL, hemoglobin 9.1 g/dL, and platelets 11,000/μL. Her PT/PTT and INR are within normal limits. She has oozing around her broviac catheter. A transfusion of platelets is ordered. The most correct statement regarding the impending transfusion is:
   A. 10 mL/kg of platelets typically raises the platelet count by approximately 25,000–30,000/μL.
   B. Platelet apheresis allows multiple units of platelets to be collected from a single donor, thereby reducing the risk of alloimmunization.
   C. Unlike packed red cell transfusions, platelet transfusions do not produce transfusion-related allergic reactions.
   D. Refrigeration of platelets allows for safe serial transfusion from the same unit.
   E. Spleen sequestration of transfused platelets rarely occurs and is not a cause of a poor response to platelet transfusion.

6. A 3-year-old in the pediatric intensive care unit with resolving sepsis and oliguric renal failure has developed persistent nose bleeds. His laboratory work up reveals the following: sodium 137 mmol/L, potassium 5.2 mmol/L, BUN 97 mg/dL, creatinine 2.7 mg/dL, WBC 5700/μL, Hb 8.2 g/dL, platelet count 102,000/μL,

INR 1.4, and aPTT 39 seconds. Of the following, which would be the most appropriate initial step to decrease the bleeding?

A. Cryoprecipitate
B. DDAVP
C. Fresh frozen plasma
D. Mannitol
E. Platelet transfusion

Answers

1. D
2. D
3. A
4. E
5. B
6. B

Suggested Readings

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Gastrointestinal

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Acute Liver Injury and Failure in Children

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Contents

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Learning Objectives

- Appreciate the varied etiologies of acute liver injury and failure in children.
- Formulate an initial management plan for the child with acute liver injury and failure.
- Initiate an appropriate diagnostic workup for pediatric acute liver failure.
- Discriminate between reversible liver injury and irreversible liver injury.
- Appreciate the need to transport children with progressive liver dysfunction to transplant centers in a timely manner prior to clinical deterioration.
- Recognize the key aspects of management and prevent complications of acute liver failure.
- Appreciate important prognostic indicators in children with acute liver failure.

42.1 Introduction

Acute liver failure (ALF) in children is uncommon. It can occur at any age and have a variety of presentations. A major challenge is to quickly determine the etiology and initiate appropriate therapy. Even with rapid diagnosis and aggressive medical management, patients may progress to irreversible liver failure and require transplantation. A multidisciplinary approach including early consultation with a transplant specialist can improve outcome. This chapter reviews the current understanding of pediatric acute liver failure (PALF) with specific attention to etiology, evaluation and diagnosis, and treatment options.

42.2 Anatomy and Physiology

Hepatic development begins at week 4 of gestation as uncommitted endoderm evolves into foregut, midgut, and hindgut. The liver, as well as lungs, gall bladder, and pancreas, are derived from the foregut. Cell differentiation and anatomic maturation continue to occur throughout gestation. Recent molecular studies suggest that as many as 20 distinct cell types may exist in the liver. However, most descriptions of hepatic function focus on four cell types: hepatocytes, endothelial cells, Kupffer cells, and stellate cells.

Hepatocytes arise from hepatoblasts and are one of the few cell types capable of regeneration. In the neonate they comprise only 20% of the liver mass, whereas by adulthood, they are the most populous cells in the liver, making up 70–80% of its mass. Hepatocytes are also one of the most diverse cells in the human body. They are involved in protein synthesis and storage, carbohydrate metabolism, synthesis and storage, and cholesterol, bile and phospholipid synthesis. Most of the metabolism and detoxification of exogenous and endogenous compounds occur in these cells. The following three cell types all line the hepatic capillary sinusoids. *Endothelial cells*, while previously thought to serve mainly a barrier function between blood and hepatocytes, are now known to mediate filtration, immunomodulation, and intra-cellular communication that may play a role in progressive liver disease, fibrosis, and even carcinogenesis. *Kupffer cells* are liver macrophages and serve to scavenge proteins, senescent red blood cells, and other cellular debris. Additionally, they secrete immune regulatory mediators that may be important in immune homeostasis. *Stellate cells* are the primary cell types responsible for hepatic architecture remodeling and fibrosis degradation. Over-activation of these cells can paradoxically lead to liver fibrosis via scarring and over-modulation of liver architecture.

Once development is complete, the liver becomes the second largest organ in the body. It is the first organ that contacts enterally absorbed nutrients and medications, via the portal vein. The portal vein delivers venous blood from the pancreas, spleen, and intestines. It also provides as much as 75% of the liver's blood supply and 50% of its oxygen supply. The hepatic arteries arise from the aorta and provide the remaining blood supply and oxygen delivery. They also deliver substances that are not metabolized during first pass as well as those introduced into circulation via nonenteral absorption. Blood leaves the liver via hepatic veins, joining the inferior vena cava on its way to the right atrium of the heart. The liver is divided into four lobes: left, right, caudate, and quadrate. Further division of the lobes into lobules is useful when describing functional units of the liver.

The biliary system is integral to hepatic function. It has both intrahepatic and extrahepatic elements. Intrahepatically, bile canaliculi between the hepatocytes drain into the canals of Herring at the edge of the liver lobules. The canals drain into the bile ducts within the portal tracts.

The intrahepatic bile ducts drain towards the hilum and bifurcate as the right and left hepatic ducts, which begin the extrahepatic biliary system. The right and left hepatic ducts join to form the common hepatic duct. The cystic duct drains the gallbladder into the common hepatic duct which then becomes the common bile duct. The common bile duct joins the main pancreatic duct to become the common hepatopancreatic duct, which ultimately drains bile into the duodenum via the ampulla of vater which is controlled by the sphincter of Oddi.

Bile consists of water, electrolytes, cholesterol, phospholipids, bile acids, and conjugated bilirubin. Once in the duodenum, bile mixes with ingested food stuffs and functions to emulsify lipids and other fat-soluble substances like vitamin A, D, E, and K, making them easier to digest and absorb. Bilirubin, a breakdown product of senescent red blood cells, is conjugated in hepatocytes and then excreted as a component of bile into the small intestine.

Hepatocytes are highly diverse cells that are not only capable of regeneration, but also function to synthesize and store carbohydrates, proteins, and fats.

42.3 Definitions and Etiologies

Acute liver failure (ALF), also known as fulminant hepatic failure or fulminant liver failure has historically been classified in adults as severe liver injury with hepatic encephalopathy developing within 8 weeks of the onset of jaundice. Pediatric acute liver failure (PALF) similarly requires severe hepatic dysfunction but does NOT require the presence of hepatic encephalopathy (HE). This is due in part to the difficulty of assessing and diagnosing HE in infants and young children. In children, especially during the newborn period, encephalopathy may not be clinically apparent and/or may be delayed in its presentation. In addition, the onset of jaundice may be insidious.

The Pediatric Acute Liver Failure Study Group (PALFSG) was founded in 1999 and initially comprised 24 domestic and international pediatric hospitals. The PALFSG was established to develop a database to facilitate study of pathogenesis, treatment and outcome of children with ALF. They developed a consensus definition of ALF in children as:

Pediatric liver failure may not develop in the same manner as in adults. Therefore, adult classification systems cannot be empirically applied to children.

- Biochemical evidence of liver injury
- No history of known chronic liver disease
- Coagulopathy not corrected with vitamin K
- INR greater than 1.5 in patient with encephalopathy or greater than 2.0 if the patient does not have encephalopathy.

Table 42.1 Causes of acute liver failure in children in the pediatric acute liver failure study group (North America and Europe)

Classification	Cause	<3 years (%)	>3 years (%)	Total (%)
Metabolic	Wilson disease, tyrosinemia, respiratory chain defect, mitochondrial disorder, galactosemia, fructose intolerance, FAOD	61 (14)	39 (8)	100 (10)
Infectious	EBV, HSV, adenovirus, HAV, HCV, enterovirus, CMV	53 (12)	28 (5)	81 (8)
APAP		13 (3)	110 (21)	123 (13)
Toxic (non APAP)	Valproate, isoniazid, dilantin, mushroom, bactrim, methotrexate	29 (6)	32 (6)	61 (6)
Autoimmune	Autoimmune hepatitis	20 (4)	48 (9)	68 (7)
Other	Shock, neonatal iron storage disease, GALD, VOD, HLH, Budd-Chiari, leukemia	48 (11)	43 (9)	91 (10)
Indeterminate	Unknown	226 (50)	218 (42)	444 (46)
Total		450 (100)	518 (100)	968 (100)

Adapted from Ng et al. for the PALFSG (2016). *EBV* Epstein Barr virus, *HSV* herpes simplex virus, *HAV* hepatitis A virus, *HCV* hepatitis C virus, *CMV* cytomegalovirus, *GALD* gestational alloimmune liver disease, *VOD* veno-occlusive disease, *HLH* hemophagocytic lymphohistiocytic histiocytosis, *FAOD* fatty acid oxidation disorder

The true incidence of PALF is difficult to determine as it may be secondary to a variety of life-threatening diseases associated with multiorgan dysfunction (e.g., sepsis and metabolic disease). Primary liver disease or injury rarely progresses to PALF. According to 2018 data from the United Network of Organ Sharing (UNOS), between 500 and 550 liver transplants are performed annually in children 0–17 years of age in the United States. Acute liver failure accounts for 10–15% of these transplants.

The etiology of PALF can be divided into several categories: metabolic, infectious, toxic, autoimmune, malignancy-induced, vascular-induced, and indeterminate (Table 42.1). Early identification of the etiologic agent allows for directed therapy and improved prognosis.

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42.3.1 Metabolic Liver Disease

Inborn errors of metabolism leading to PALF may be seen in all ages but are most often encountered in children less than 1 year of age.

Inborn errors of metabolism leading to PALF may be seen in all ages but is most often observed in children less than 1 year of age. In the neonatal period, galactosemia, hereditary fructose intolerance, tyrosinemia, neonatal hemochromatosis, and ornithine transcarbamylase (OTC) deficiency can present with hypoglycemia, coagulopathy, lactic acidosis, failure to thrive, and irritability. Patients with urea cycle defects may present with an initial respiratory alkalosis and severe hyperammonemia. Regardless of etiology, if liver failure is advanced, lactic acidosis is often present due in part to the loss of hepatic

lactate metabolism. Jaundice may be present, depending on the extent of hyperbilirubinemia. Inborn errors of metabolism are typically associated with a conjugated hyperbilirubinemia. Galactosemia and tyrosinemia type I may cause refractory coagulopathy in the infant with minimal other signs of liver failure. Symptomatic metabolic liver disease may present before the results of newborn screening are available.

Mitochondrial disorders usually present with multiorgan dysfunction involving the liver, kidneys, brain, neuromuscular system, and heart. In children with mitochondrial disorders, the severity of liver dysfunction can vary from mild to severe. The constellation of hypoglycemia, lactic acidosis, neurological symptoms, and muscle and renal tubular dysfunction is highly suggestive of a mitochondrial disorder.

Fatty acid oxidation disorders (FAOD) include long chain fatty acid transport defects, as well as short, medium and long chain co-enzyme defects. Key features of FAOD are hypoglycemic episodes with low to absent urine ketones and liver dysfunction with mild to moderate hyperammonemia.

The exact nature of the inborn error will not only affect the initial management but will impact decisions regarding the suitability for transplantation.

It is imperative that infants with a suspected metabolic cause for ALF have a prompt and comprehensive diagnostic evaluation. The exact nature of the inborn error will not only affect the initial management but will impact decisions regarding the suitability for transplantation. For example, a child with a urea cycle defect failing medical management may be a candidate for liver transplantation, whereas a child with a severe mitochondrial disorder and multisystem organ involvement may not.

Wilson disease is not seen in the newborn period but is the most common metabolic cause of ALF in children older than 5 years of age.

The presentation of Wilson disease in the newborn or infant period is unusual. In contrast, it is the most common metabolic cause of ALF in children older than 5 years of age. Wilson disease is caused by a defect in hepatocellular copper transport, leading to the accumulation of copper in the liver and extrahepatic organs, particularly the central nervous system. A child may present with nonspecific symptoms of fever, fatigue, and progressive jaundice. Eye examination using a slit lamp may reveal Kayser–Fleischer rings. Laboratory evaluation reveals hemolytic anemia, hyperbilirubinemia, and a low to normal serum alkaline phosphatase. Serum and urinary copper levels are elevated while serum ceruloplasmin levels are low. Mortality for fulminant Wilson disease reaches 100% without liver transplantation; therefore, early diagnosis and referral is essential.

42.3.2 Infection Induced Liver Disease

Acute liver failure in a child with prodromal symptoms such as fever, myalgia, poor appetite, and fatigue may be secondary to infection. Worldwide, hepatitis A is the most frequent infectious cause of PALF due to its high prevalence in developing countries. A review of over 4000 children with acute hepatitis in Argentina revealed that hepatitis A was the overall leading cause of PALF. Mortality can reach 50% in hospitals where liver transplantation is not available. In North America and Europe, hepatitis A is infrequent in children and is usually benign, but 0.5–1% of infections may evolve into liver failure. Ongoing immunization for hepatitis A continues to lower the incidence of infection induced PALF.

Hepatitis B as a cause of PALF is infrequent in children in developed countries due in large part to successful immunization programs. While more commonly a disease of the adult population, it may occur in the neonatal period after peri-partum infection. High risk behaviors such as intravenous drug abuse place adolescents at risk for hepatitis B associated PALF.

Hepatitis C, D, and G rarely cause PALF. Hepatitis E is endemic in many areas such as India and Mexico but does not commonly lead to liver failure.

Herpes simplex virus can cause severe PALF and is the most common viral etiology in infants less than 3 months of age. This disease is often rapidly progressive and can be associated with encephalopathy, profound coagulopathy, and multisystem organ dysfunction. Other herpes viruses (HHV – 1, 2, 6) have been associated with PALF in immunocompromised patients.

Parvovirus B19 in the setting of aplastic anemia has been associated with PALF but it remains uncertain if this relationship is causal. Hemolytic anemia as well as hemophagocytic syndrome has been associated with Epstein Barr Virus. Echovirus, adenovirus, enterovirus, and varicella have also been reported in cases of PALF but rarely in the immunocompetent host.

Bacterial causes are rare. Exotoxin-related liver damage has been reported with group A streptococcal infections, the rare case leading to liver failure.

Parasitic infections are endemic in many countries worldwide, but rarely lead to PALF. An exception is malaria, which has been reported to cause ALF in children and adults.

42.3.3 APAP Induced Liver Injury

Acetaminophen (APAP) toxicity is the most common cause of PALF due to drug ingestion. This is particularly true in developed countries where its use is widespread. In younger children, overdose is usually due to incorrect dosage administration by the caregiver or accidental ingestion by the child. In the adolescent population, it is often an intentional ingestion. Ingestion of greater than 140 mg/kg can be toxic. The biochemical basis of APAP hepatotoxicity, presentation, and management is discussed in detail in ▶ Chap. 46 Toxicology for the Pediatric Intensivist.

Acetaminophen toxicity is the most common cause of PALF due to drug ingestion.

Hepatotoxicity is dependent on the stage of APAP toxicity, commonly divided into four stages. Early signs and symptoms include anorexia, nausea/vomiting, and malaise, and transaminases may still be normal. In the ensuing 24–72 h after ingestion, jaundice, coagulopathy, and encephalopathy can occur, and it is during this time that transaminases typically rise dramatically. Serum bilirubin may be normal or elevated. Fatalities are uncommon since the advent of N-acetylcysteine (NAC) and the widely accepted use of the Rumack nomogram (◘ Fig. 46.1). While very useful in predicting potential toxicity, the nomogram should only be applied when the time of a single ingestion is known.

Use of the Rumack-Matthew Nomogram can be useful in predicting potential APAP toxicity but should only be applied when the time of a single ingestion is known.

42.3.4 NonAPAP Induced Liver Injury

Medication related liver damage is uncommon in children when not associated with an overdose, however a variety of drugs have been associated with idiosyncratic reactions causing liver injury. Antiepileptic drugs (AEDs) account for a significant portion of nonAPAP induced drug injury. Valproic acid may cause direct damage to hepatic mitochondria. Other AEDs such as phenytoin, carbamazepine and phenobarbital have been associated with a hypersensitivity reaction that can range from a mild cutaneous rash to life-threatening organ failure.

Previously known as DRESS (drug reaction with eosinophilia and systemic symptoms), the triad of fever, rash and systemic organ involvement suggests anticonvulsant hypersensitivity syndrome (AHS). The interval between drug exposure and symptoms is usually 2–4 weeks but can be delayed up to 3 months. Other drugs with the potential for severe hepatotoxicity include volatile anesthetics, propylthiouracil and sulfa containing compounds.

A triad of fever, rash and systemic organ involvement in a patient taking one or more antiepileptic drugs should prompt suspicion of anticonvulsant hypersensitivity syndrome.

Herbal medications and dietary supplements have been shown to cause drug induced liver injury that may progress to PALF. An exact delineation of the most prominent herbal compounds that cause PALF has been problematic due to a variety of reasons. Many herbal preparations contain a multitude of organic compounds, thus making the implication of a single compound difficult. Due to the lack of regulatory oversight, herbal medications may be contaminated with unknown compounds. Lastly, clinicians may overlook the history of herbal medication use and may label the cause of PALF as undetermined. Certain herbal compounds such as black cohosh and chaparral have been linked with the development of adult and PALF. A history of herbal medication and dietary supplement use should be sought in any child with presenting ALF.

42.3.5 Amatoxin Induced Liver injury

Ingestion of a mushroom-related toxin may present after a 6–24 h latency period with nonspecific gastrointestinal symptoms resulting in delayed diagnosis and potential development of serious dehydration and circulatory collapse.

Ingestion of wild mushrooms, particularly the amanita species and its related amatoxin can cause PALF. Patients may have a 6–24 h latency period after ingestion. Initial symptoms are consistent with a mild, transient gastroenteritis–like illness. Diagnosis is often delayed due to its insidious onset and the potential for the misdiagnosis as a flu-like illness. Worsening gastrointestinal pain with nausea, vomiting, and profuse watery diarrhea prompts medical attention. Dehydration with electrolyte abnormalities and circulatory collapse may ensue. Early detection is of great clinical importance since decontamination with activated charcoal can substantially limit the amount of toxin absorbed from the GI tract.

42.3.6 Autoimmune Liver injury

The etiology of autoimmune hepatitis (AIH) in children is poorly understood. Several viruses including EBV, measles, and hepatitis A and C have been implicated for triggering the immune-regulated destruction of hepatocytes.

Autoimmune hepatitis is generally classified into three types based on biomarkers and age predominance. Extra-hepatic disease commonly co-exists. Type II AIH is the most common type seen in younger populations and is associated with anti-liver-kidney-muscle antibodies.

Autoimmune hepatitis is responsible for 1–5% of PALF. It typically presents as progressive inflammatory liver disease. In newborns, giant cell hepatitis associated with hemolytic anemia may progress to ALF. In older children, the etiologies are more diverse. There are three classifications of AIH distinguished by specific biomarkers and age group predominance.

Type I AIH is associated with antinuclear antibodies (ANA) and/or smooth muscle antibodies. Patients may be positive for perinuclear antineutrophilic cytoplasmic antibodies. This type of AIH is often termed the "classic" form. It has bimodal peak incidence at 10–20 years of age and 45–70 years of age with a female predominance of 3.6:1. Many patients have extra hepatic diseases such as Grave's disease, ulcerative colitis, rheumatoid arthritis, or idiopathic thrombocytopenia purpura.

Type II AIH is associated with anti-liver-kidney-muscle antibodies. It is less common than type I and predominates in the younger population (2–14 years of age). It is rarely diagnosed in adults. As with type I, extra hepatic diseases are common such as diabetes mellitus, thyroiditis, and vitiligo.

Type III AIH is associated with anti-soluble liver antigen, smooth muscle antibodies, and anti-liver membrane antigen. Less common are mitochondrial antibodies and rheumatoid factor. These patients are negative for ANA or anti-liver-kidney-muscle antibodies. It is a disease that occurs almost exclusively in adults.

42.3.7 Miscellaneous Causes of Liver injury

PALF may manifest shortly after birth. Gestational alloimmune liver disease (GALD) is a disease process mediated by maternal IgG antibodies (directed against fetal hepatocytes) that are actively transported across the placenta to the fetus leading to subsequent severe liver injury. Recent data has revealed that the hepatocyte damage in cases of neonatal hemochromatosis (NH) is most consistent with complement mediated injury. It is now believed that GALD is the cause of liver injury that leads to most cases of NH. While GALD is not always associated with iron deposition in the liver, NH does lead to accumulation of iron within hepatocytes as well as extra-hepatic tissues. These neonatal forms of PALF can cause progressive multiorgan failure and cirrhosis.

Vascular induced PALF can occur as a result of Budd-Chiari syndrome (obstruction of hepatic venous outflow) or veno-occlusive disease (hepatic vein occlusion following bone marrow transplantation or chemotherapy). Shock states resulting in prolonged liver ischemia or hypoxia can lead to irreversible liver injury. Celiac disease, sclerosing cholangitis, and infiltrative malignancies may also rarely lead to PALF.

In the child suspected of having hemophagocytic lymphohistiocytosis, hypertriglyceridemia, elevated ferritin level and hemophagocytosis on bone marrow examination will aid in confirming the diagnosis.

Lymphoproliferative diseases that lead to massive liver infiltration can cause ALF. Over the last 15 years, hemophagocytic lymphohistiocytosis (HLH) has been increasingly recognized as a cause of multisystem organ dysfunction including hepatic failure. The primary type (familial) of HLH is inherited in an autosomal recessive pattern and usually occurs in the first few years of life. Secondary HLH (acquired) is associated with infections (i.e., usually EBV), autoimmune disorders, or malignancies (lymphoma). Acquired HLH can occur at any age. Clinical presentation for both types is similar with fever, splenomegaly, jaundice, histiocytosis, and cytopenia (affecting >= 2 of 3 cell lines). Hypertriglyceridemia, high ferritin levels, hemophagocytosis on bone marrow histology, and lymphocytosis in CSF can aid in the diagnosis.

The etiology of ALF in children remains undetermined in as many as 30–50% of cases.

42.4 Clinical Presentation

The clinician should pay close attention to pertinent positive and negative findings that may aid in early identification of the cause, leading to the initiation of focused and specific therapies.

The clinical presentation of children with ALF is variable depending on age and etiology. Most children are healthy prior to the onset of liver impairment and have no antecedent risk factors for liver disease. Symptoms usually progress rapidly over a few days to weeks, and profound deterioration of a previously healthy child is not uncommon. A detailed and accurate history and physical exam is essential. The clinician should pay close attention to pertinent positive and negative findings that may aid in early identification of the cause (i.e., medication and toxin exposures, infectious symptoms, and other organ system involvement), leading to the initiation of focused and specific therapies.

Questions regarding the history of present illness should focus on the onset and duration of symptoms including change in mental status, fever, vomiting, pruritus, abdominal pain, weight loss or gain, and bruising. Inquiries should be made about exposure to persons possibly infected with hepatitis or recent international travel. In the adolescent population, time spent in a detention center or engaging in illicit drug use or sexual activity are relevant questions. A complete history regarding the use of over the counter prescription or herbal medications and dietary supplements is necessary. A family history of autoimmune or hereditary diseases, as well as infantile deaths, may help to narrow the diagnosis.

Table 42.2 Grades of hepatic encephalopathy

I	Changes in behavior, minimal change in level of consciousness, altered sleep (hypersomnia), insomnia, inverted sleep cycle in the newborn
II	Spatiotemporal disorientation, drowsiness, inappropriate behavior, obvious asterixis
III	Marked confusion, stuporous, may or may not respond to auditory stimuli, responds to pain, asterixis usually absent
IV	Comatose, unresponsive to pain

Adapted from the West Haven criteria. Atterbury et al. (1978)

Initial examination should focus on signs of respiratory distress, hemodynamic instability, or rapidly changing mental status. After stabilization, inspection for nutritional status, jaundice, hepatosplenomegaly, needle marks, caput succedaneum, petechiae, purpura, ascites, and peripheral edema should be done. Older children require an ophthalmologic exam to rule out the presence of Kayser–Fleischer rings.

Assessment of the child's mental status should be done serially throughout the hospital course. An initial grading of the encephalopathy has important clinical and prognostic implications. Hepatic encephalopathy (HE) is a neuropsychiatric syndrome associated with liver dysfunction that is graded by severity according to specific exam findings (Table 42.2). This grading system was initially applied to adults with liver cirrhosis but has since been adapted to describe the degree of encephalopathy in children. Hepatic encephalopathy can occur within a few hours to days after the onset of jaundice. Both jaundice and HE are less useful as prognosticators in the very young child or infant. In the newborn, signs of HE are nonspecific and may only be noticed as subtle behavior changes or increased agitation. An unusual or high-pitched cry may be appreciated. Electroencephalography (EEG) may be used to monitor the degree of encephalopathy. A recent study by the PALF Study Group revealed that while mortality or need for a liver transplant is highest in children with grade III or IV HE, death may occur in children with ALF and no clinical evidence of HE.

Both jaundice and hepatic encephalopathy are less useful as prognosticators in the very young child or infant.

The presence of HE requires close monitoring for signs and symptoms of progressive cerebral edema. Patients with HE can deteriorate very rapidly. Early signs of cerebral edema such as behavioral changes or somnolence may be missed, particularly in infants and young children. Late and ominous findings consistent with progressive cerebral edema include the presence of altered muscle tone, elevated blood pressure with relative bradycardia, irregular respiratory pattern, seizures, extreme agitation or lethargy, and any focal cranial nerve abnormality such as loss of gag, cough, or unequal pupils.

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42.5 Diagnostic Evaluation

The goal of the diagnostic evaluation is to establish an etiology as rapidly as possible while defining the severity of the liver failure. The diagnostic approach often involves a battery of laboratory tests unless a specific etiology is evident upon presentation (i.e., acetaminophen toxicity or infectious hepatitis). Table 42.3 summarizes a systems-based laboratory and imaging evaluation of PALF.

Table 42.3 Diagnostic evaluation of children with acute liver failure

System	Laboratory and imaging
Hematologic	CBC, PT/PTT, INR, fibrinogen, d-dimer, reticulocyte count, factor II, V, VII, VIII, IX, X, type/screen, serum ferritin
Renal	BUN, Cr
Electrolytes	Na, K, Cl, Mg, Phos, Ca
Hepatic	AST, ALT, AP, GGT, LDH, total and direct bilirubin, ammonia, lactate, glucose, triglycerides
Pancreatic	Amylase, lipase, abdominal ultrasound
Cardiopulmonary	Blood gas, echocardiogram, ECG, CXR
Neurologic	Brain imaging, EEG
Metabolic	Serum copper and ceruloplasmin, ferritin and salivary gland biopsy, lactate, pyruvate, succinyl acetone, urine for copper and organic acids, muscle/liver/bone marrow biopsy, mitochondrial DNA
Infectious	Cultures (serum, urine, respiratory, stool, CSF), antigen and antibody serologies for hepatitis A, B, C, E, PCR for HHV 6, HSV, CMV, EBV, parvovirus B19, echovirus, enterovirus, adenovirus
Toxic	Serum and urine toxicology screen, acetaminophen and salicylate level, blood and urine to be held on ice for later investigations
Autoimmune	Coombs test, ANA, RF, AIH antibodies and antigens, pANCA, NK cell function

CBC complete blood count, *PT* prothrombin time, *PTT* partial thromboplastin time, *INR* international normalization ratio, *AST* aspartate transaminase, *ALT* alanine transaminase, *AP* alkaline phosphatase, *GGT* gamma glutamyl transferase, *LDH* lactate dehydrogenase, *EEG* electroencephalogram, *CXR* chest x-ray, *CSF* cerebrospinal fluid, *PCR* polymerase chain reaction, *HHV* human herpes virus, *CMV* cytomegalovirus virus, *EBV* Epstein Barr virus, *ANA* antinuclear antibody, *RF* rheumatoid factor, *AIH* autoimmune hepatitis, *pANCA* perinuclear antineutrophil cytoplasmic antibody, *NK* natural killer

Initial laboratory evaluation should include serum electrolytes, blood gas, complete blood count, blood typing, transaminases, fractionated bilirubin, ammonia, and evaluation of hepatic synthetic function (PT, PTT, albumin). Measurements of certain coagulation factors deserve specific mention. Factors V and VII are synthesized only by hepatocytes. Serial measurements of factors V and VII have been used to prognosticate the likelihood of PALF progressing to end stage liver failure and need for transplantation. Because Factor VII has a short circulating half-life of approximately 4–8 h, it may be a more sensitive indicator of worsening hepatocellular injury when measured serially. Factor VIII is produced within the liver and extra-hepatically in the vascular endothelium. Recent data suggests that the lung microvasculature may be a prominent site of factor VIII production. Because a significant portion of factor VIII is produced extrahepatically, its measurement can help delineate if a coagulopathy is primarily due to hepatocellular failure versus a consumptive process such as disseminated intravascular coagulation (DIC). During ALF induced coagulopathy, factor VIII levels are preserved due to their extrahepatic production whereas if the coagulopathy is primarily due to DIC, levels will be depleted.

During ALF induced coagulopathy, serum levels of factors VII and VIII can help discriminate between acute hepatocellular injury and DIC.

Rising alpha fetoprotein (AFP) levels have traditionally been used to detect hepatic recovery. Newer data suggests that an AFP ratio comparing day 1 to day 3 levels may be a better marker for survival.

An investigation for infectious hepatitis (e.g., Hep A-G, HHV 1, 2 and 6, CMV, EBV, echovirus, enterovirus, adenovirus and parvovirus B19, and syphilis) should include viral cultures and serologies. Blood, urine, CSF, and stool bacterial cultures should also be obtained.

Toxicological investigation should include rapid determination of acetaminophen, aspirin, and alcohol levels followed by comprehensive urine and blood toxicology screens. Coombs test, ANA, RF, and various other antibody and antigen markers, as detailed earlier, may be required to rule out autoimmune hepatitis.

Serum amino acids, lactate, pyruvate, ammonia, and urine organic acids should be obtained early to investigate possible inborn errors of metabolism. Ferritin level should be obtained in the child with suspected hemochromatosis or HLH. Salivary gland biopsy may reveal extrahepatic iron deposition. Serum ceruloplasmin, serum, and urinary copper levels are required in the older child to rule out Wilson disease. Other metabolic studies obtained when indicated include CSF lactate (mitochondrial cytopathy) and muscle biopsy. Ultimately, a liver biopsy may be required but should be deferred until a normalized coagulation profile is achieved. Similarly, CSF studies should be deferred until hemostasis is present and there is no evidence of cerebral edema.

An abdominal ultrasound and echocardiogram can be useful to identify ascites, vascular patency and assess cardiac function. Brain imaging and an EEG should be obtained when hepatic encephalopathy is clinically suspected. Despite the often extensive and costly diagnostic evaluation, the etiology of ALF in children remains undetermined in 30–50% of cases.

Despite extensive diagnostic evaluation, the etiology of ALF in children remains undetermined in 30–50% of cases.

42.6 Monitoring and Management of Complications

The care of a child with ALF requires admission to a PICU. If the initial PICU admission occurs in an institution without pediatric transplant capabilities, the nearest transplant center should be contacted early since the only definitive treatment for progressive liver failure is a liver transplant.

Monitoring may include arterial, central venous, and intracranial pressure measurements. Guidelines for the general care of PALF exist, with different centers augmenting certain parameters according to their experiences. General supportive care is similar regardless of the etiology (◘ Table 42.4). Specific therapies for PALF with known etiologies are summarized in ◘ Table 42.5.

42.6.1 Hepatic Encephalopathy and Cerebral Edema

The presence of HE in PALF merits aggressive treatment and serial monitoring. The grade of encephalopathy can change rapidly, requiring the care provider to make rapid decisions and implement care designed to prevent elevations in ICP while maintaining adequate CPP. Any patient with PALF who has a sudden change in mental status should have immediate bedside glucose determination, neurological examination assessing for signs of cerebral edema, and ammonia determination. An urgent head CT is necessary if no easily correctable metabolic cause for the change in mental status is identified. If signs of cerebral edema are evident, ICP lowering therapies should be initiated prior to imaging. Advanced stages of HE (stage 3 or 4) are often associated with airway compromise and endotracheal intubation is generally recommended. Determining the need for these interventions can be even more challenging in the newborn or infant who may not reveal obvious signs/symptoms of progressive encephalopathy.

The grade of encephalopathy can change rapidly, requiring the care provider to make quick decisions and implement care designed to prevent elevations in ICP.

Table 42.4 Medical management of pediatric acute liver failure – supportive care

Supportive care	
Hepatic encephalopathy (Hyperammonemia)	Decreased protein intake (1.2–1.5 g/kg/day)
	Lactulose 10–15 ml/kg/day oral/rectal – goal 2–3 loose stools/day
	Sodium benzoate, sodium phenylacetate, arginine
	Hemofiltration
	Avoid medications solely dependent on hepatic metabolism
Cerebral edema	ICP and cerebral hemodynamic invasive monitoring
	ICP precautions – see text for details
Coagulopathy	Vitamin K SQ/IV daily
	FFP – bleeding or planned invasive/surgical procedure
	Platelets – platelet count <50,000 with bleeding or <10,000 without bleeding
	Plasmapheresis, plasma exchange
Renal failure and nutritional support	Avoid nephrotoxic drugs
	CRRT with or without dialysis
	Hyper alimentation if unable to take enteral nutrition
	Glucose infusion 10–15 mg/kg/min
Cardiopulmonary failure	Arterial, CVP, SvO2 monitoring
	Maintain adequate MAP to prevent organ ischemia

ICP intracranial pressure, *SQ* subcutaneous, *IV* intravenous, *FFP* fresh frozen plasma, *CRRT* continuous renal replacement therapy

There are two main theories regarding the relationship between ALF and cerebral edema; the glutamine hypothesis (cytotoxic edema) and cerebral vasodilation hypothesis (vasogenic edema). Under normal conditions, ammonia metabolism occurs in multiple organs including the liver, kidney, and skeletal muscle. Hepatic enzymes convert ammonia and carbon dioxide into urea, which can then be excreted by the kidneys. The kidneys can also excrete ammonia directly. When hepatic urea synthesis is impaired, circulating ammonia levels increase. To prevent toxic hyperammonemia, there is a compensatory increase in skeletal muscle production of glutamine, which complexes with unbound ammonia to form the more stable compound, glutamate.

There are two main theories regarding the relationship between ALF and cerebral edema, the glutamine hypothesis (cytotoxic edema) and cerebral vasodilation hypothesis (vasogenic edema).

Glutamine is also synthesized in brain astrocytes. Increased astrocytic production of glutamine may occur in response to decreased hepatic urea production. Elevated astrocytic glutamine levels lead to an increase in cellular osmolality, favoring the development of cytotoxic edema (Fig 42.1). Direct astrocyte damage can also occur when intracellular glutamine is converted back into glutamate and ammonia. High intracellular levels of ammonia can lead to mitochondrial damage and apoptosis.

Table 42.5 Medical management of pediatric acute liver failure – disease specific care

Disease specific care of acute liver failure	
Metabolic disorders	
GALF, NH	Double volume exchange transfusion
	IVIG 1 g/kg
Wilson disease	Copper chelation Plasmapheresis
Hereditary tyrosinemia	Nitisinone 1 mg/kg/day orally in two doses
Fatty acid oxidation defect	IV glucose and avoid fasting
Galactosemia	Removal of galactose from diet
Inherited fructose intolerance	Removal of fructose from diet
Infections	
Herpes virus	Acyclovir 150 mg/m^2/day IV
Hepatitis B virus	Interferon alpha
	Entecavir
	Tenofovir
Cytomegalovirus	Ganciclovir 10 mg/kg/day IV
Bacterial	Antibiotics as indicated; Gram positive prophylaxis optional
Fungal or parasitic	Antifungal and/or antiparasitic as indicated
Toxic ingestions	
Basic interventions	Activated charcoal depending on toxin and time of ingestion
Acetaminophen poisoning	N-acetyl-cysteine IV 150 mg/kg over 15 min, then 50 mg/kg over 4 h, then 100 mg/kg over 15 h
Mushroom poisoning	Penicillin G 300,000–1 million units/kg/day IV
	Silymarin 30–40 mg/kg/day IV or oral
Autoimmune disorders	
Autoimmune hepatitis	Prednisone 2 mg/kg/day (max 60 mg/day) IV or oral
	Azathioprine 0.5 mg/kg/day (max 2 mg/kg/day) IV or oral
Other	
Shock	Basic life support followed by fluid resuscitation, vasopressor support and prevention of multiorgan failure
HLH	Steroids
	Chemotherapeutics
	IVIG
	Bone marrow transplant
VOD	Defibrotide
	Diuresis; CRRT
	Prevention of hyperbilirubinemia toxicity
	Transfusion of platelets and coagulation factors
Malignancy	Chemotherapy and/or radiation as indicated

IV intravenous, *HLH* hemophagocytic lymphohistiocytosis, *VOD* veno-occlusive disease

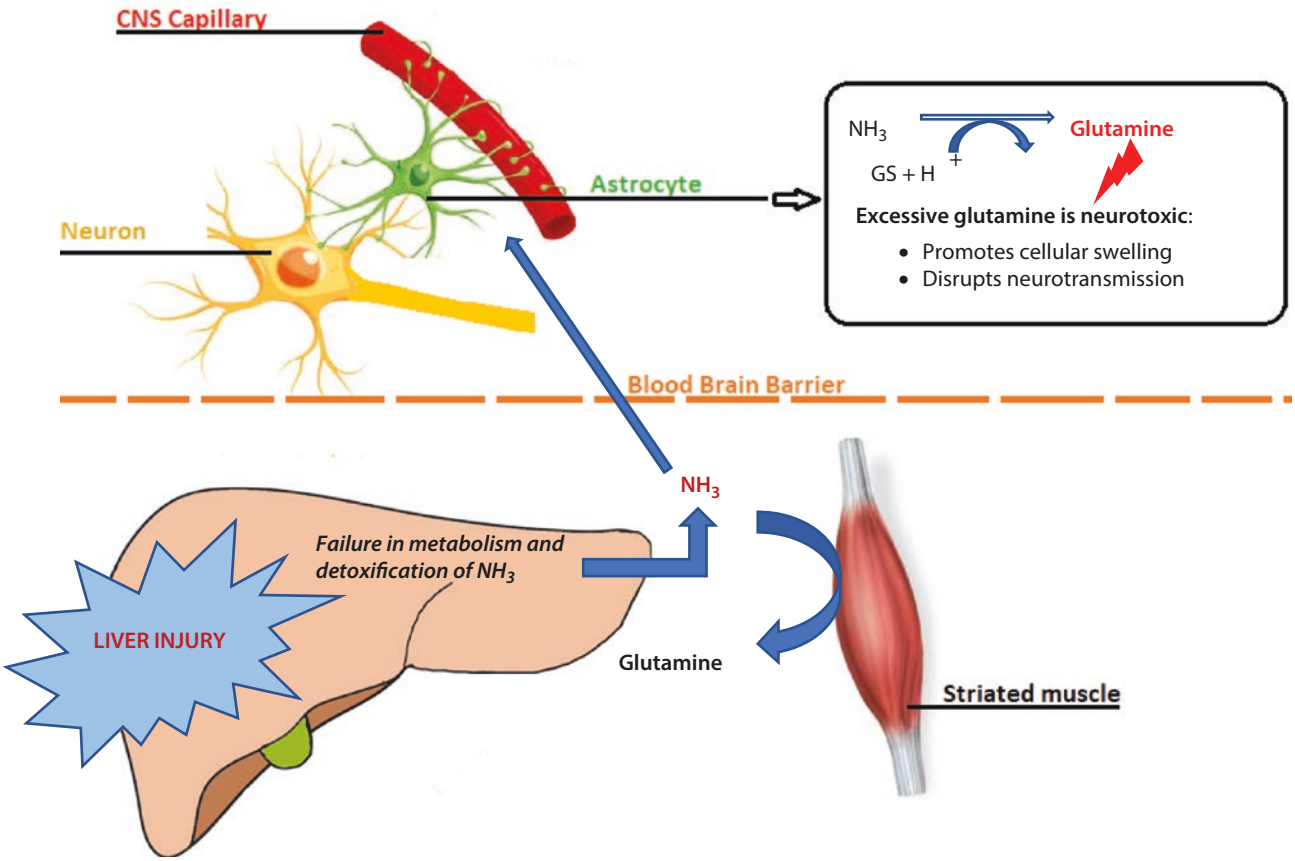

Fig. 42.1 Liver failure results in decreased metabolism of ammonia within the urea cycle leading to the accumulation of ammonia in the systemic circulation. Ammonia readily crosses the blood–brain-barrier. CNS ammonia detoxification occurs via glutamine synthetase (GS), exclusively expressed in astrocytes. Normally, the formation of glutamine acts as a precursor of the main excitatory and inhibitory neurotransmitters glutamate and gamma-hydroxybutyric acid (GABA), respectively. However, excessive astrocytic glutamine is a potent osmolar agent and causes cellular swelling. In addition, glutamine accumulation induces changes in cerebral neurotransmission. (Courtesy FA. Maffei)

Vasogenic edema may further contribute to cerebral swelling in patients with ALF. Disordered cerebral autoregulation can lead to cerebral arteriolar dilation and hyperemia. Hyperemia coupled with low oncotic pressure, primarily from hypoalbuminemia, favors a fluid shift from intravascular to interstitial tissues. Alterations in blood–brain barrier (BBB) permeability has also been hypothesized to contribute to vasogenic edema. The exact mechanisms remain unclear, but animal studies suggest that protein deregulation at endothelial tight junctions may allow increased permeability to water and other small molecules. Animal models demonstrate increased levels of enzymes (metalloproteinase family of endopeptidases) released from the injured liver are associated with tight junction dysfunction. Additionally, human and animal studies have found an association between high levels of proinflammatory cytokines (IL-1B, IL-6, TNF-a) present in sepsis patients with ALF. These cytokines may contribute to ongoing neuroinflammation and the development of cerebral edema.

42.6.2 Management of Hyperammonemia and Elevated ICP

Increased serum ammonia levels are common in children with HE. However, not all children with ALF and HE will develop hyperammonemia. The normal level of serum ammonia ranges: 160–340 mcg/dl in newborns, 65–130 mcg/dl

in children up to 2 years of age, and 20–60 in children older than 2. While hyperammonemia is worrisome, there is no clear data to suggest a therapeutic cutoff for initiating an intervention such as endotracheal intubation, ICP precautions, or specific hyperammonemia treatments, to name a few. If present, initial treatment of hyperammonemia should focus on the prevention of ongoing excess ammonia production. Earlier recommendations to limit protein intake to no more than 0.5 g/kg/day have recently been called into question by studies demonstrating improved protein retention and decreased protein catabolism with administration of 1.2–1.5 g/kg/day through the enteral or parenteral route. Lactulose and lactitol are nonabsorbable disaccharides which when metabolized by gut flora acidify the intraluminal colonic environment trapping ammonia in its less soluble, polar form ammonium (NH4+). As osmotic agents, these disaccharides allow "captured" luminal ammonium to be excreted in stool. They are well tolerated and are considered first-line treatments for hyperammonemia with considerable evidence for efficacy. Caution must be used to prevent excess stooling and loss of water and electrolytes. Enteral administration of antibiotics (neomycin or metronidazole) can reduce ammonia production by reducing urea splitting intestinal flora; however, the current literature does not support their routine use.

Several therapies have been used to bind with or facilitate metabolism of serum ammonia and increase urinary ammonia excretion. These include sodium benzoate, sodium phenylacetate, phenylbutyrate and arginine. Their usage should be guided by a hepatologist or metabolic specialist. The most effective way to clear ammonia from a patient's serum is by hemodialysis. Indications for hemodialysis include refractory hyperammonemia with progressive HE, fluid overload >10% body weight despite the use of diuretics and hepatorenal syndrome. Continuous dialysis is preferred over intermittent dialysis.

The most effective method to eliminate ammonia is through hemodialysis.

Progression to advanced HE is associated with high mortality. Cerebral autoregulation is lost in grade 4 encephalopathy and is likely impaired in the earlier stages. Concern for elevated ICP requires discussions regarding potential benefits versus risks of invasive ICP monitoring. Although pediatric data is scarce and studies to date have not shown a statistical improvement in outcome in adults with ALF receiving ICP monitoring, it may be useful as a guide to management. Patients who are waiting for liver transplant may benefit from an ICP monitor once coagulopathy has been corrected.

Guidelines to treat elevated ICP in PALF are similar to those utilized in treating traumatic brain injury. The head of bed should be elevated to at least 30°. The child should be placed in a quiet environment with sedation as necessary to decrease cerebral metabolic demand. Narcotics and benzodiazepines should be used with caution due to impaired metabolism. Lower starting doses are recommended. Remifentanil, a short acting synthetic derivative of fentanyl, is metabolized by plasma and RBC esterases. Since it does not undergo hepatic metabolism, it can be used safely even in patients with advance liver failure. Refractory intracranial hypertension may benefit from short-acting barbiturates. Osmotherapy with a sodium target range of 145–155 meq/L or higher has been shown to be effective in lowering ICP but has not been shown to improve mortality. Hyperventilation is useful for emergent treatment of elevated ICP with impending herniation but is not recommended as a routine therapy. Mannitol or hypertonic saline can be used in the event of an acute rise in ICP. Hypothermia has not been consistently proven to be of benefit and has several potential risks such as further immune and coagulation dysfunction; however, fever should be avoided as it can elevate cerebral metabolic demand.

42.6.3 Coagulopathy

The liver is responsible for the synthesis of most of the procoagulant and anticoagulant factors (excluding III, IV, and VIII). Synthetic dysfunction is present in virtually all cases of advance PALF. While an elevated PT/INR and PTT may reflect losses in coagulant factors due to tissue and endothelial injury, the deficiency or dysfunction of procoagulant factors are difficult to quantify using standard coagulation testing. Therefore, PT/INR alone is not useful in assessing the relative risk of bleeding.

Recent literature has investigated the use of thromboelastography (TEG) to determine the bleeding risk in patients with ALF. Thromboelastography is a viscoelastic test that allows rapid evaluation of clot formation and fibrinolysis from a sample of whole blood. It has gained support in guiding blood product resuscitation in children and adults with severe trauma. Recent adult data suggests that there is a low risk of bleeding when TEG values are normal. Of note, data regarding the use of TEG for risk stratification for children with ALF and significant bleeding episodes is limited.

Bleeding is uncommon in PALF and if bleeding does occur, etiologies include gastric erosions/ulcers, varices or any regions of mucosal disruption. Prevention of infections, avoidance of NSAIDs and reducing portal hypertension will decrease the likelihood of a gastrointestinal hemorrhage. Daily Vitamin K is recommended in patients that have an abnormal PT/INR. Correcting the coagulopathy to a normal PT/INR is unnecessary and may even be dangerous. Although the use of TEG has potential utility, FFP should be considered for marked coagulopathy (INR > 7) without bleeding, active bleeding regardless of INR or if an invasive procedure or surgery is planned.

Occult bleeding is uncommon in PALF despite often profoundly abnormal coagulation indices. PT/INR alone is not useful in assessing the relative risk of bleeding. TEG may provide more clinically useful information about both coagulation and fibrinolysis

Recombinant factor VIIa should be reserved for emergent correction or in cases where volume overload precludes FFP administration. Platelet infusion may be indicated in patients with severe thrombocytopenia (<10,000) or <50,000 with active bleeding. Disseminated intravascular coagulation (DIC) may also be present, placing the patient at an increased risk for hemorrhage and thromboses. Plasma exchange with hemofiltration has been used to correct coagulopathy while improving fluid balance.

42.6.4 Nutritional and Metabolic Support

The most common metabolic abnormality encountered in PALF is hypoglycemia. Hypoglycemia occurs as a result of impaired gluconeogenesis, exhausted glycogen stores, or as a primary manifestation of an inborn error of metabolism. The state of heightened stress that occurs during PALF leads to increased glucagon and growth hormone release, further increasing the carbohydrate catabolism. The breakdown of fats and proteins provides necessary cellular energy but leads to a loss of adipose and muscle tissue, as well as increased fatty acids and urea by-products.

Glucose needs are usually quite high and may require central access so that IV fluids with high dextrose concentration can be administered. A glucose infusion rate between 10 and 15 mg/kg/min is recommended. Recent data has demonstrated improved protein retention and decreased protein catabolism with protein administration as high as 1.2–1.5 g/kg/day through the enteral or parenteral route.

Careful fluid management includes restriction of total fluid intake and the use of loop diuretics to avoid fluid overload especially in the child at risk cerebral edema.

Electrolyte abnormalities are common with hyponatremia, hypokalemia, hypophosphatemia, hypocalcemia, and hypomagnesemia potentially complicating management. The causes of such electrolyte abnormalities are multifactorial and include hormone dysregulation, fluid overload, renal losses, and

increased catabolism. Unless contraindicated, enteral nutrition is recommended. Hyperalimentation may be used but can place additional metabolic demands on the liver. Caloric needs may be increased by as much as 20% over the basal metabolic rate. Careful fluid management includes restriction of free water intake and the use of loop diuretics to avoid fluid overload especially in the child at risk for cerebral edema. Invasive monitoring of arterial pressure and CVP can help guide fluid management.

Acid base abnormalities can also occur and are usually mixed. Metabolic acidosis from shock, hepatic necrosis, and increased anaerobic metabolism may occur. Decreased liver clearance of organic acids and lactate is usually associated with a compensatory respiratory alkalosis. Additionally, respiratory alkalosis may occur secondary to ammonia induced hyperventilation.

42.6.5 Cardiopulmonary Support

The child with ALF may present with normal hemodynamics or in fulminant shock. Low systemic vascular resistance is common and may lead to tachycardia and a high cardiac output state. Hyperdynamic circulation associated with liver cirrhosis and portal hypertension has been well documented in adults. While there are many mediators that contribute to the low SVR state, endothelial shear stress from portal hypertension is implicated as a potent stimulator of nitric oxide (NO) production. Elevated NO contributes to systemic vasodilation and the potential development of hepatorenal syndrome (see below). After appropriate volume resuscitation, the institution of a vasopressor such as norepinephrine may be required to maintain adequate mean arterial pressure. Although direct myocardial dysfunction is uncommon, an electrocardiogram, echocardiogram, and cardiac troponin level should be performed if cardiac injury is suspected. Cardiac dysfunction should be addressed immediately with preload and inotropic support titrated to clinical response as determined by improved organ perfusion.

Low SVR and resultant high output cardiac failure may occur and is associated in part with increased endogenous nitric oxide production.

Patients may experience adrenal insufficiency from a prolonged stress state. Baseline cortisol level followed by ACTH stimulation can identify patients in whom stress-dosed hydrocortisone may be beneficial.

Hypoxemia is common and usually multifactorial. Increased circulating vasodilatory substances blunt the normal hypoxia-mediated pulmonary vasoconstriction, worsening ventilation-perfusion mismatch. This loss of vascular autoregulation can increase the risk of pulmonary edema. Centrally-mediated neurogenic pulmonary edema can also complicate pulmonary function. Progressive pulmonary dysfunction coupled with neurologic deterioration often warrants mechanical ventilation. Delivery of oxygen to tissues in most cases is adequate, but there may be decreased oxygen uptake at the cellular level leading to elevation in central or mixed venous saturations. Pulmonary dysfunction coupled with defective oxygen uptake at the tissue level can lead to refractory hypoxemia and lactic acidosis.

Pulmonary dysfunction coupled with defective oxygen uptake at the tissue level can lead to a persistent and often refractory hypoxemia and tissue oxygen debt.

42.6.6 Renal Failure

Renal failure is less frequent in PALF when compared to adult ALF (15–20% vs. 45%). It can occur within the context of hepatorenal syndrome or as a result of direct injury from medications, sepsis, hemorrhage and shock, or excessive fluid restriction. Hepatorenal syndrome (HRS) is a life-threatening condition that is more common in chronic liver failure and cirrhosis. However, it can occur in the presence of ALF and progress rapidly over 1–2 weeks. HRS can

Hepatorenal syndrome is often associated with low serum and urine sodium, elevated urine creatinine, and elevated urine osmolality. Tubular nephropathy can lead to electrolyte losses of sodium, phosphorous, magnesium, and potassium.

result in impaired tubular and cortical function with oliguria or anuria. The etiology of HRS, in part, is thought to be due to liver injury-induced altered renal perfusion and vascular tone via release of local vasodilators, such as nitric oxide, into the splanchnic and systemic circulation. This is known as the "underfill" theory. Based on this theory, the over-circulation that occurs in the splanchnic vasculature leads to a relative decrease in renal perfusion. This results in activation of the renin-angiotensin-aldosterone system. Both systemic and renal vasoconstriction occurs causing glomerular filtration and sodium excretion to decrease. The increased absorption of sodium (mediated by aldosterone) is believed to be a major contributor to the development of ascites. Unlike with prerenal azotemia, the serum and urine sodium are typically low in HRS. Elevated urine creatinine and osmolality are also frequently seen in HRS. Tubular nephropathy can occur resulting in hypophosphatemia, hypomagnesemia, and hypokalemia.

Protective strategies include maintaining adequate renal perfusion and minimizing exposure to toxic medications. Judicious diuresis, despite the presence of ascites, is recommended. Adult evidence suggests combination therapy with an alpha-1 adrenoreceptor agonists (midodrine) or vasopressin analogues (terlipressin) and albumin repletion can ameliorate symptoms of HRS.

In CVVHDF, solute removal occurs via both convection and diffusion utilizing high flow ultra-filtration and hemodialysis.

Continuous renal replacement therapy (CRRT) allows filtration and/or hemodialysis by using varying flow rates. CRRT is well tolerated even in hemodynamically unstable patients. There are three types of CRRT circuits that can be utilized in the patient with ALF. The first is continuous venovenous hemofiltration (CVVHF) which provides solute removal via convection and offers high flow ultra-filtration. The second is continuous venovenous hemodialysis (CVVHD) which incorporates dialysate flow that is countercurrent to the flow of blood across the semi permeable membrane and provides solute removal via diffusion. Lastly, continuous venovenous hemodiafiltration (CVVHDF) promotes solute removal via both convection and diffusion utilizing high flow ultra-filtration and hemodialysis. A single institution study involving 22 children with at least grade III HE and awaiting liver transplant showed that high volume CVVHF improved hemodynamics at 24 h and decreased the severity of HE at 48 h. Despite its ability to rapidly remove ammonia, correct acidosis, restore electrolyte abnormalities, and maintain euvolemia, no pediatric studies to date show a statistically significant reduction in mortality over standard medical care.

While the definitive treatment for HRS is liver transplantation, molecular adsorbents recirculation system (MARS) has proven beneficial in preserving renal function. There is limited data for a renal-protective effect of N-acetylcysteine in children with HRS.

42.6.7 Immune Dysfunction and Infections

Children with ALF have an increased susceptibility to infections due to a dysregulation of immune function. This is related to a deficiency of complement and opsonin as well as neutrophil dysfunction. In addition, newer data suggests that cytotoxic T cells may have an impaired ability to contain the inflammatory response present in most cases of ALF, leading to additional liver injury and possible loss of normal regeneration.

The most common opportunistic organism to cause bacteremia in these patients is *Staphylococcus aureus*. Fungal infections may also occur. Signs of progressive sepsis may be subtle and unappreciated to the baseline phys-

iologic derangements that are common in patients with advanced liver failu r e .
The typical systemic inflammatory response syndrome (SIRS – tachycardia, tachypnea, leukocytosis, and temperature instability) seen in most patients with a serious infection may be lacking due to the down-regulated immune response.

In advanced liver failure, the low SVR state may mimic vasodilatory shock. Fever may be absent. Therefore, any signs of clinical deterioration or evidence of compromised end organ perfusion such as decreased urine output or change in mental status should prompt a search for infection. There is no consensus on the use of prophylactic antibiotics (broad spectrum cephalosporin and/or antifungal agent) in PALF. However, if clinical suspicion for infection is high, particularly in patients with SIRS and grade 3 or 4 HE, antibiotics covering both gram-positive and gram-negative organisms as well as antifungal agents may be started after cultures are obtained. Additionally, the more frequent need for invasive lines and procedures places the child with ALF at risk for nosocomial infections.

42.6.8 Liver Support Devices

When medical therapies fail to reverse the process of liver destruction, the options are limited to transplant or devices that can temporarily support the function of the liver while awaiting transplant. In rare cases, supporting the function of the liver for a short time period may allow delayed recovery making liver transplant unnecessary. Most of the experience with liver support devices over the last several decades have occurred in adults. However, there are several devices that have been utilized in children with ALF. The main challenge of these systems is to duplicate the complex functions of a healthy liver. Bioartificial liver support utilizes a system of hollow fibers that are impregnated with human hepatocytes. The patient's blood is then circulated through this "artificial liver." Adult data suggests improved survival in select patient populations.

In rare cases, temporary mechanical support of the failing liver can allow recovery.

The molecular absorbent recirculating system (MARS) has been used extensively in adults and less frequently in PALF. Blood is circulated through a system utilizing albumin and semi permeable membranes in a step-wise process. First, an albumin based-hemodialysis circuit removes protein-bound molecules and toxins. The blood then flows through a column that removes the now albumin-bound toxins and reactivates the albumin for further use in the body. A recent pediatric case series of 20 children with ALF treated with MARS demonstrated significantly lower levels of ammonia, bile acids, bilirubin, and creatinine. In addition, MARS successfully lowered serum copper, iron and phenol levels. This application is best used for PALF associated with hyperbilirubinemia, hepatorenal syndrome, or patients with MODS. Despite the ability of mechanical extracorporeal devices to remove harmful by-products of liver dysfunction, a recent review of randomized trials of artificial and bio-artificial support systems for acute liver failure concluded that the use of these systems does not appear to decrease mortality.

Plasma exchange (PE) has been shown to decrease serum ammonia, improve coagulation profile, and lessen encephalopathy and in one adult RCT trial led to improved survival over standardized treatment. The data is less favorable in PALF. While PE has led to an improved coagulation profile in children, it has not improved survival.

42.6.9 Transplant

Children with ALF who have failed medical treatment or require ongoing mechanical liver support due to end-stage liver failure will need a liver transplant to survive. Overall, liver transplant has resulted in improved survival for children with ALF. Regional transplant centers have 1-year survival rates as high as 90%. Newborns and smaller children may not tolerate a whole liver and have done well with split and cut-down liver transplants. Recent data revealed higher survival rates (1, 5 and 10 year) in children who received a living donor transplant compared to those from a deceased donor.

42.6.10 Prognosis

In adult liver failure, the prognosis for survival, and ultimately the decision to proceed to transplant has been largely based on prognostic modeling. The earliest of these was based on criteria developed at King's College in London in 1989 and is known as King's College Criteria (KCC). This model was developed to determine if there were clinical features or specific tests that correlated with prognosis. In addition, the criteria were stratified into acetaminophen and nonacetaminophen causes of ALF (Table 42.6). While this model continues to be utilized to guide decision making in adults, it is less suited for the pediatric population.

Table 42.6 King's College criteria for liver transplantation

Cuse of acute liver failure	Criteria
Acetaminophen ingestion	Arterial pH < 7.3 (irrespective of the grade of encephalopathy)
	Or
	Grade III or IV encephalopathy
	And
	Prothrombin time > 100 s (INR > 6.5)
	And
	Serum creatinine > 3.4 mg/dL
All other causes	Prothrombin time > 100 s (INR > 6.5)
	Or three of the following
	Age <10 or >40 years
	Non A, non B hepatitis, halothane hepatitis, idiosyncratic drug reactions
	Duration of jaundice before onset of encephalopathy >7 days
	Prothrombin time > 50 s (INR > 3.5)
	Serum bilirubin > 18 mg/dL

Adapted from the King's College criteria for liver transplantation in fulminant hepatic failure. O'Grady et al. (1989)

The model for end-stage liver disease (MELD) is a scoring system originally developed to predict the outcome in patients with chronic liver disease undergoing transjugular intrahepatic portosystemic shunt (TIPS) procedure. It was eventually found to be useful in selecting optimal candidates for liver transplant. In 2002, UNOS began using this model for organ allocation. MELD incorporates INR, serum creatinine, and serum bilirubin into a formula to calculate a number associated with the risk of death (high numbers equate to higher risk). Cirrhosis as an etiology was originally included into the calculus but further research determined that this inclusion limited its applicability and removing cirrhosis from the equation did not decrease its accuracy. In addition, the model could now be based on purely objective laboratory values. Head to head comparisons between KCC and MELD models suggest utility for both approaches. A recent meta-analysis found that the KCC was a better predictor for hospital mortality in adults with acetaminophen related ALF while MELD better predicted outcome in patients with nonacetaminophen related ALF.

A pediatric model for end-stage liver disease (PELD) also exists, and in fact, was implemented by UNOS the same year as MELD. The pediatric model is applied to children 11 years of age and younger. Recognizing the specific growth and development needs of young children, this scoring system incorporates the presence or absence of growth failure and whether the child is less than 1 year of age. It also includes serum albumin while removing serum creatinine. However, this model applies to children with chronic liver disease and has not shown the same predictive utility in PALF. The PALFSG data continues to be analyzed and interpreted by researchers around the world. One analysis of this data evaluated KCC criteria in nonacetaminophen PALF and showed that it did not reliably predict death. While research is ongoing and new scoring systems are being tested, there currently exists no scoring model or objective criterion that can reliably predict mortality in children with ALF.

Although not a validated pediatric prediction model, the presence of one of the following physiologic derangements adapted from the KCC, should prompt a consultation and or transfer to a liver transplantation center:

- Acidosis (admission arterial pH < 7.30) OR
- Hepatic encephalopathy (grade III or IV), AND coagulopathy (PT > 100 s), and acute kidney injury (creatinine > 3.4 mg/dL), OR
- Hyperlactatemia (4-hour lactate > 3.5 mmol/L, or 12-hour lactate > 3.0 mmol/L), or
- Hyperphosphatemia (phosphate > 3.7 mg/dL at > 48 h post ingestion)

While several additional risk stratification models and serum biomarkers exist to further define hepatotoxicity, the serum APAP level multiplied by the highest aminotransferase level (AST or ALT) may hold promise as a new risk predictor following paracetamol overdose. Often, the time of ingestion may not be known, or ingestion may have occurred over several hours/days. In these cases, the Rumack nomogram may not be useful in predicting hepatotoxicity. Additionally, metabolism of APAP varies depending on the severity of hepatic injury, not to mention the confounding effect co-ingestions may contribute. Many have raised concerns that solely utilizing a nomogram based on APAP levels in response to NAC treatment may lack sensitivity to identify patients who are poor responders or underestimate the severity of hepatic injury. Utilizing data collected by the Canadian Acetaminophen Overdose Study (CAOS), authors examined patients with an AST or ALT > 1,000 IU/L who had a known single ingestion of APAP with a measured APAP level at least 4 h post ingestion. To better identify patients at risk for developing hepatotoxicity and perhaps inform real-time management decisions, they developed a tool

that consists of the multiplication of simultaneously measured APAP and highest AT value. The product of this multiplication (APAP X AT) was analyzed at the start of NAC and several times during its treatment course. Increasing levels predicted peak INR values, and correlated with worsening hepatotoxicity that would be traditionally identified by worsening AT levels. However, the multiplication product is not restricted to single ingestions or those with known time of ingestions. The same authors later examined data from a large cohort of patients admitted to hospitals in the United Kingdom. They found that a product of >10,000 mg/L × IU/L was associated with a very high likelihood of developing hepatotoxicity, whereas values <1,500 mg/L × IU/L were not. This was independent of the ingestion type. This tool may be of use to guide patient management in cases of APAP overdose, particularly when the time of ingestion is unknown.

Etiology is among the most important determinant of outcome. For example, fulminant Wilson disease carries a uniformly fatal prognosis without liver transplant. An undetermined diagnosis has been associated with poor outcomes. Multiple studies have demonstrated elevated ammonia, hyperbilirubinemia, or coagulopathy to be sensitive predictors of outcome. Certain underlying conditions or co-morbidities preclude eligibility for transplant. Malignancies and mitochondrial disorders are a contraindication. Advanced MODS and refractory intracranial hypertension are associated with severe morbidity and very high mortality leading many centers to defer liver transplantation.

Underlying etiology, biomarkers reflective of degree of liver injury and stage of encephalopathy remain the best predictors of short-term outcome.

Advances in understanding of the pathophysiology and treatment of infection-induced and toxin-related PALF has also contributed to better outcomes. Meticulous supportive care during PALF makes spontaneous recovery a viable option. In cases where a "bridge" to transplant is needed, improving technology is increasing both the quality and life span of transplant candidates.

42.7 Summary

Acute liver failure in children is a relatively rare disease. There are multiple causes that are specific to certain age groups while most can occur in both children and adults. The etiology of the largest percentage of PALF cases remains undetermined. Patients with PALF require admission to a PICU with constant collaboration between medical and transplant specialists. Early identification of etiology, meticulous supportive care, and prompt consultation with a liver transplant center are the cornerstones of care for the child with ALF and may ultimately lead to improved overall survival.

Review Questions

1. Which of the following statements is true regarding the presentation of pediatric acute liver failure (PALF)?
   A. A history of chronic liver disease does not affect the prognosis of PALF.
   B. Bleeding and coagulopathy are the presenting symptoms of PALF secondary to the ingestion of amatoxin (wild mushrooms).
   C. Hepatic encephalopathy is often the initial symptom of acetaminophen-induced liver failure.
   D. In infants, encephalopathy may be absent up to 12 weeks after the initial symptoms.
   E. Jaundice is always present in cases of newborn ALF.

2. Which of the following statements is true regarding Wilson disease?
   A. Elevated serum copper and ceruloplasmin levels are characteristic of the disease.

B. It is the most common metabolic disease presenting with ALF during infancy.
C. Kayser-Fleischer rings may be detected on slit lamp examination of the eyes.
D. Laboratory evaluation commonly reveals hemolytic anemia, hyperbilirubinemia, and an elevated serum alkaline phosphatase.
E. Mortality from fulminant Wilson disease is unusual; however, in rare cases, liver transplantation has been performed with success.

3. Which of the following inborn errors of metabolism associated with PALF is LEAST likely to present during the neonatal period?
A. Galactosemia
B. Hereditary fructose intolerance
C. Ornithine transcarbamylase (OTC) deficiency
D. Tyrosinemia
E. Wilson disease

4. Which of the following is the most common infectious cause of PALF worldwide?
A. Bacterial endotoxin
B. Hepatitis A Virus
C. Hepatitis B Virus
D. Human Herpes Virus
E. Malaria

5. Which of the following is NOT an effective and recommended treatment option for hyperammonemia associated with PALF?
A. Hemofiltration/Hemodialysis
B. Lactulose
C. Minimizing protein intake to less than 0.1 g/kg/day
D. Neomycin
E. Sodium Benzoate

6. Based on the two theories that describe the relationship between ALF and cerebral edema, which of the following is not correct?
A. Increased serum ammonia concentrations occur as hepatic metabolism becomes impaired.
B. Astrocyte swelling may occur as intracellular ammonia is detoxified to glutamine.
C. Disordered cerebral autoregulation typically leads to cerebral arterial constriction and subsequent cerebral hypovolemia.
D. Kidney function is important in the clearance of ammonia.
E. Elevated inflammatory cytokines and cellular tight junction disruption occurs in ALF similarly to sepsis and plays a role in worsening cerebral edema.

7. Which of the following therapies is indicated for the prevention of PALF secondary to acetaminophen toxicity?
A. Hemodialysis
B. Intravenous glutamate
C. Intravenous glutathione
D. Intravenous N-acetylcysteine
E. Intravenous sodium benzoate

8. Which of the following therapies is indicated for the treatment/prevention of PALF secondary to hepatic veno-occlusive disease?
   A. Cyclosporine
   B. Defibrotide
   C. Deferoxamine
   D. Hemodialysis
   E. Silymarin

9. Which one of the following tests would be most helpful in distinguishing liver disease from disseminated intravascular coagulation (DIC) as the cause of a coagulopathy?
   A. Activated partial thromboplastin time
   B. Bleeding time
   C. Factor VIII level
   D. Prothrombin time
   E. Thrombin time

10. Which of the following is the most likely hemodynamic alteration to be observed in a patient with late acute liver failure?
   A. Decreased stroke volume due to poor ventricular filling
   B. Hyperdynamic myocardium with low systemic vascular resistance
   C. Increased pulmonary and systemic vascular resistance
   D. Increased renal blood flow
   E. Preserved cerebral autoregulation

11. Which of the following is the most common metabolic abnormality encountered in PALF?
   A. Hypocalcemia
   B. Hypoglycemia
   C. Hypokalemia
   D. Hyponatremia
   E. Hypophosphatemia

12. Which of the following statements is true regarding immune function and infection in PALF?
   A. Clinical symptoms of infection are often subtle, and therefore, any clinical deterioration should prompt a thorough search for infection.
   B. Given the defects in the immune system, fungal infections are common in acute liver failure, but gram-positive bacteremia is rare.
   C. Immune dysfunction is characterized by a deficiency of complement and opsonin, but essentially normal neutrophil function.
   D. Sepsis is a relatively uncommon complication of acute liver failure.
   E. The need for invasive catheters and procedures is the only risk factor for sepsis among these children.

Answers

1. D
2. C
3. E
4. B
5. C
6. C
7. D

8. B
9. C
10. B
11. B
12. A

Suggested Readings

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Endocrine and Metabolic

Contents

Critical Care Endocrinology

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Learning Objectives

- Describe the signs and symptoms of endocrine/metabolic disturbances
- Discuss the mechanisms important in maintaining glucose homeostasis
- Identify the common causes of hypoglycemia in infants and children
- Summarize how to evaluate and treat the child who presents with hypoglycemia
- Describe the pathophysiology of diabetic ketoacidosis
- Summarize the evaluation, management, and monitoring of the child who presents with diabetic ketoacidosis
- Summarize the evaluation and management of the child who presents with hyperglycemic hyperosmolar state
- Describe how to diagnose and preoperatively manage children with pheochromocytomas
- Discuss the controversies that exist when diagnosing adrenal insufficiency in a critically ill child
- Describe how to treat the child with known or suspected adrenal insufficiency
- Describe the current modalities available for the treatment of hyperthyroidism in children
- Summarize the biochemical and pathophysiological differences between thyroidal and nonthyroidal illnesses
- Identify the causes and treatment of disorders of calcium homeostasis
- Describe how to evaluate, manage, and monitor the child with diabetes insipidus, syndrome of inappropriate antidiuretic secretion, and cerebral salt wasting
- Recognize disturbances of osmoregulation encountered in patients with tumors of the central nervous system both pre- and postoperatively

43.1 Introduction

Endocrine emergencies may present as isolated occurrences, as the initial manifestation of an endocrine disorder, or as an acute decompensation in the condition of a child with a known endocrine disease that resulted from noncompliance with medication or the stress of an intercurrent illness. Signs and symptoms of endocrine disorders may be nonspecific and may include altered level of consciousness, respiratory changes, and alterations in muscle tone. A history of poor feeding, vomiting, weight loss, or lethargy may also be elicited. When evaluating a child with a suspected endocrinologic abnormality, it is imperative to obtain baseline laboratory samples prior to treatment such that the proper diagnosis and treatment can expeditiously be determined.

43.2 Hypoglycemia

In normal individuals, glucose concentration is maintained at ~80 mg/dL in the basal state and rises briefly to levels of no more than 150 mg/dL shortly after a feeding, returning to levels below 140 mg/L within 2 h after the feeding. The major hormone facilitating the normal return of postprandial glucose concentration is insulin, secreted by β-cells of the islets of Langerhans in the pancreas. During overnight fasting, glucose concentration is maintained through the activation of glycogenolysis, gluconeogenesis, and inhibition of glycogen synthesis mediated by suppression of insulin and the coordinated

Table 43.1 Hormonal regulation of fasting metabolic systems

	Hepatic glycogenolysis	Hepatic gluconeogenesis	Adipose tissue lipolysis	Hepatic ketogenesis
Insulin	–	–	–	–
Epinephrine	+	+	+	+
Glucagon	+	+		+
Cortisol		+		
Growth Hormone			+	

A (–) sign indicates inhibition; a (+) sign indicates activation of the indicated process

actions of the counter-regulatory hormones: glucagon secreted by α-cells of the islets, cortisol from the adrenal cortex, growth hormone by the pituitary, and catecholamines from the adrenal medulla and sympathetic nervous system. More prolonged fasting leads to activation of lipolysis and ketogenesis; muscles, including cardiac muscle, can utilize fatty acids and/or ketones, sparing glucose primarily for the brain, which cannot metabolize fatty acids. In this way, glucose production is precisely matched to glucose utilization, even during exercise. A rise in counter-regulatory hormones, such as catecholamines, glucagon, cortisol, and growth hormone, contributes to this regulation of glucose homeostasis, while insulin concentration is low (Table 43.1). After feeding, insulin concentration rises for 1–2 h to levels 5–10 times basal, and the levels of counter-regulatory hormones fall. This hormonal profile enables glycogen synthesis in liver and muscle, lipid synthesis in fat tissue, and protein anabolism in muscle.

The adult brain accounts for more than one-half of total glucose consumption. Since the brain in infants and young children is relatively large compared to the remaining body mass, their glucose utilization rate per kg body weight is two- to fourfold higher compared with adults. In the postabsorptive state, more than 4 h after feeding, the rate of glucose turnover in adults is approximately 2 mg/kg/min whereas the average basal (4–6 h after feeding) rate of glucose turnover is 5–8 mg/kg/min in newborns, three to four times the adult weight-based rate. Infants and younger children also have smaller reserves of liver glycogen and muscle protein. These developmental differences in glucose requirements and utilization in infants and younger children make them more prone to developing hypoglycemia when subjected to a prolonged fast or when an underlying pathologic condition of glucose regulation is present. These considerations have relevance to the status of glucose homeostasis in infants and children in an intensive care unit (ICU) setting where the child may be under considerable stress.

The clinical definition of hypoglycemia is defined as a plasma glucose concentration low enough to cause symptoms and/or signs of impaired brain function. Hypoglycemia cannot be defined based on a specific plasma glucose concentration because (1) thresholds for specific brain responses to hypoglycemia occur across a range of plasma glucose concentrations, and the threshold can be altered by the presence of alternative fuels such as ketones, and by recent antecedent hypoglycemia (as explained below); (2) it is not possible to identify a single plasma glucose value that causes brain injury, and the extent of brain injury is determined by other factors such as metabolic demand (e.g.,

temperature) and the duration of hypoglycemia; and (3) potential artifacts and technical factors can affect glucose measurement leading to inaccuracies. In general, symptoms typically appear when the glucose concentration is <60–70 mg/dL.

Hypoglycemia may be difficult to recognize clinically because the signs and symptoms are nonspecific and a single low glucose concentration may be an artifact (see below). Adult recommendations suggest that the Whipple triad is useful to confirm hypoglycemia: symptoms and/or signs consistent with hypoglycemia, a documented low plasma glucose concentration at the time of symptoms, and relief of signs/symptoms when plasma glucose concentration is restored to normal. Since younger children and infants may not be able to communicate the resolution of symptoms, repeated confirmation of low plasma glucose concentration and formal testing (fasting) may be needed to confirm the diagnosis.

When suspected, hypoglycemia should be confirmed using a clinical lab technique. In the ICU, there are several potential artifacts in measurement that need to be considered. Although commonly used and convenient, point-of-care (POC) testing is limited in accuracy to ±10–15 mg/dL in the concentration range when hypoglycemia occurs. If a serum sample is sent to the lab in a tube without an inhibitor of glycolysis, ongoing red blood cell glycolysis can reduce the glucose concentration by up to 6 mg/dL/h; high hematocrit and increased sample temperature will accelerate glycolysis. If a whole blood glucose sample is measured, the values are ~15% lower than plasma glucose concentrations.

The clinical signs and symptoms of hypoglycemia may be blunted by previous exposure to hypoglycemia; repeated episodes can eliminate the neurogenic (autonomic) responses to subsequent hypoglycemia episodes. This leads to reduced or absent awareness of hypoglycemia and impairs hepatic glucose release, perpetuating hypoglycemia. This combination of events has been termed hypoglycemia-associated autonomic failure (HAAF), which can persist for >24 h after a single episode of hypoglycemia or even longer after repeated episodes.

Hyperinsulinism is a significant cause of hypoglycemia in infants and children and is the most common cause of persistent hypoglycemia in the neonatal period.

Hyperinsulinism may be caused by inactivating mutations of the K_{ATP} channel, exogenous administration of glucose-lowering medications, or by an insulin-secreting adenoma.

Neonates may have a normal transitional period of hypoglycemia; however, a diagnostic evaluation is warranted in the neonatal period if hypoglycemia persists beyond the 2–3 day transitional period. Prolonged hypoglycemia (>48 h) may be due to more common causes of perinatal hyperinsulinism, such as birth asphyxia, intrauterine growth restriction, preeclampsia, and maternal diabetes, or may be due to rare conditions such as congenital hyperinsulinism. Hyperinsulinism is a significant cause of persistent hypoglycemia in infants and children and is the most common cause of hypoglycemia in the neonatal period. Hyperinsulinism may be caused by activating mutations of enzymes, such as glucokinase and glutamate dehydrogenase, by inactivating mutations of the K_{ATP} channel regulating insulin secretion, by exogenous administration of glucose-lowering medications such as insulin or sulfonylureas, or by an insulin-secreting adenoma. Hyperinsulism is characterized by insulin concentrations usually >2–3 μIU/mL and C-peptide >0.5 ng/mL when the glucose concentration is less than 50 mg/dL; characteristically, ketones and free fatty acids are low or undetectable. Since ketones are an alternate fuel source for the brain and are low or absent in this setting, hyperinsulism-induced hypoglycemia may increase the risk for brain injury.

Ketotic hypoglycemia is a common cause of childhood hypoglycemia and usually presents between 18 months and 5 years; symptoms usually resolve by 8–9 years. Hypoglycemic episodes usually occur following periods of fasting (e.g., a prolonged illness that impairs oral intake). Parents may report a history

Table 43.2 Causes of hypoglycemia in infancy and childhood

Hyperinsulinism
Deficiencies of counterregulatory hormones (cortisol, growth hormone, catecholamines, glucagon)
Ketotic hypoglycemia
Glycogen storage diseases
Galactosemia
Disorders of gluconeogenesis
Disorders of fatty acid oxidation
Hereditary fructose intolerance
Drug-induced hypoglycemia (insulin, sulfonylureas, alcohol, β-adrenergic blockers, and salicylates)
Glucose transporter deficiencies

of morning lethargy or seizure activity. Ketonemia and/or ketonuria are usually present at the time of documented hypoglycemia. Concurrent insulin levels are low (<2 μIU/mL), thereby excluding hyperinsulinism.

Deficiencies of counterregulatory hormones may cause hypoglycemia. Individuals at risk include those with congenital or acquired panhypopituitarism (with subsequent ACTH and/or growth hormone deficiency), adrenal disorders (e.g., congenital adrenal hyperplasia [CAH], Addison's disease, adrenoleukodystrophy), and, rarely, epinephrine and glucagon deficiencies as might occur with β-adrenergic blockers or diffuse pancreatic disease in cystic fibrosis, respectively.

Children with glycogen storage diseases oftentimes present in late infancy or childhood with persistent hypoglycemia in association with hepatomegaly and failure to thrive but without symptoms of hypoglycemia. The absence of symptoms occurs because their brains have adapted to chronic hypoglycemia by utilizing lactate and ketone bodies.

Approximately one-fourth of normal children develop hypoglycemia after a fast of 24–36 h duration. With increasing age, carbohydrate regulation improves as higher levels of gluconeogenic substrates are available.

Children with hypoglycemia associated with a gastrointestinal illness have depletion of hepatic glycogen stores and reduced availability of free fatty acids and ketones. Hypoglycemia is a major cause of death, especially in underdeveloped countries where malnutrition is common, and where bacterial pathogens are responsible for a considerable proportion of cases of acute gastroenteritis.

Postprandial hypoglycemia is a relatively common and often unrecognized complication following a Nissen fundoplication for gastroesophageal reflux (incidence 25–30%). In these patients, hypoglycemia often occurs 1–3 h after a meal and is often preceded by an exaggerated glucose and insulin response.

Other less common causes of hypoglycemia are listed in Table 43.2.

43.2.1 Laboratory Evaluation

Obtaining a critical sample at the time of hypoglycemia will yield crucial diagnostic information. Once hypoglycemia is suspected, a baseline sample for measurement of glucose, ketones, free fatty acids, insulin, cortisol, and growth

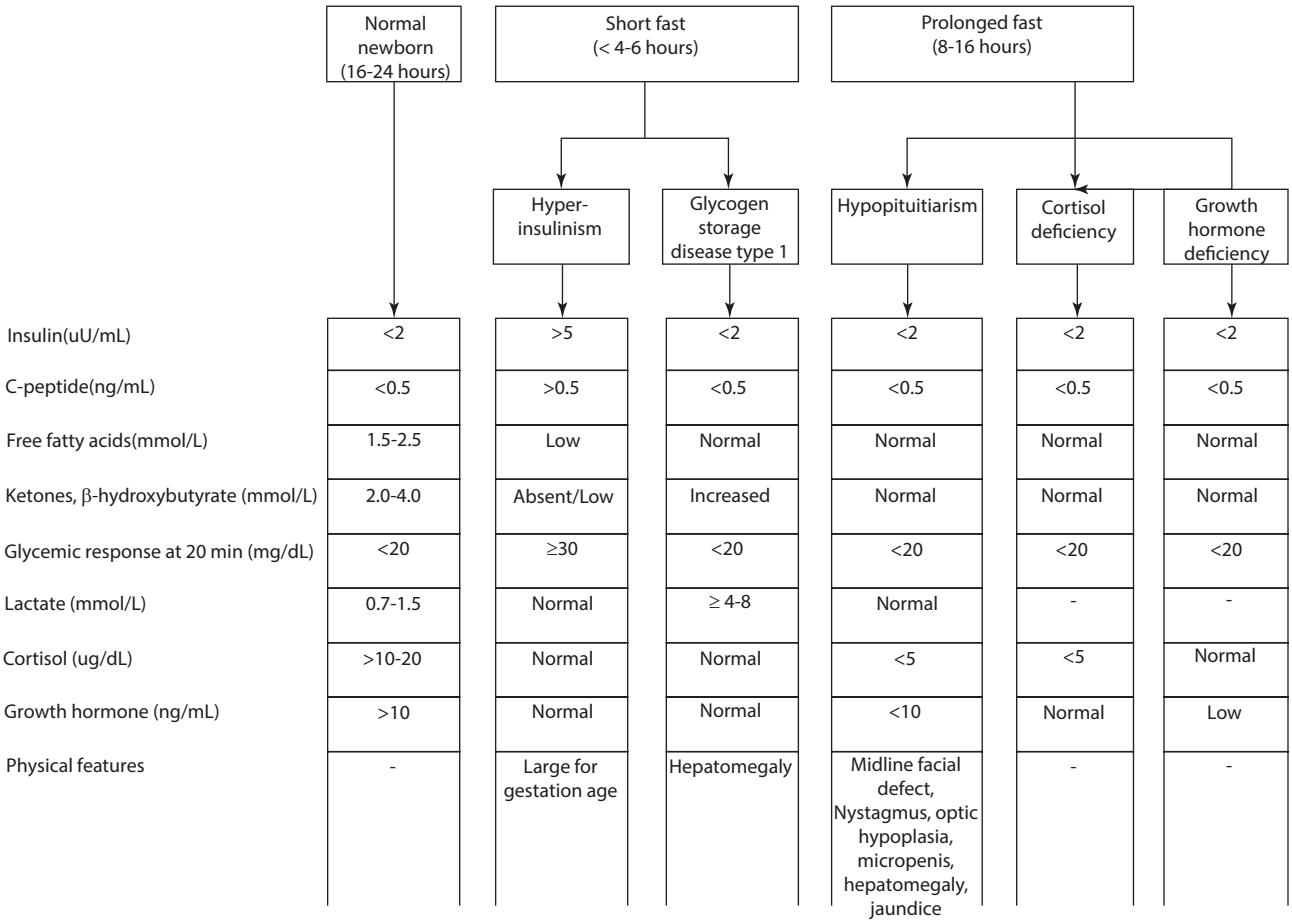


Fig. 43.1 Algorithmic approach to differential diagnosis of major causes of neonatal hypoglycemia based on duration of fasting. Hypoglycemia is defined as blood glucose <50 mg/dL

hormone must be obtained *before* treatment with glucose is given. Priority of testing should be tailored to each individual patient based on a thorough history. Basic studies should include a confirmatory plasma glucose (i.e., placed on ice and often in a tube containing a glycolysis inhibitor), chemistry panel with bicarbonate, beta-hydroxybutyrate, lactate, ammonia, cortisol, growth hormone, and insulin or C-peptide concentrations. Urine may also be examined for ketones, but urinary ketone testing only measures acetoacetate and does not detect the major ketone, β-hydroxybutyrate. If a fatty acid oxidation defect is suspected, further studies such as an acyl carnitine profile or urine organic acid measurements can be obtained. An algorithmic approach to differential diagnosis of major causes of neonatal hypoglycemia is provided in Fig. 43.1.

Obtaining a critical blood sample at the time of hypoglycemia, including a plasma glucose and insulin/C-peptide level, chemistry panel with bicarbonate, beta-hydroxybutyrate, lactate, ammonia, growth hormone, and cortisol concentrations, will yield important diagnostic information. An archival sample (blood and urine) may also be obtained for additional future testing.

43.2.2 Treatment

In neonates, once the critical sample has been obtained, 0.2–0.25 g/kg intravenous dextrose should be administered (usually achieved with 2.5 mL/kg of 10% dextrose solution) followed by a continuous infusion of about 5–8 mg/kg/min of dextrose. A lower infusion rate of 4–6 kg/kg/min is recommended and associated with improved neurodevelopmental outcomes in asymptomatic high risk neonates (maternal diabetes, large for gestational age, fetal growth restriction, and/or prematurity). The dextrose infusion rate may be increased to 15–25 mg/kg/min as needed to maintain euglycemia. Glucagon can be used for acute management in cases of insulin-induced hypoglycemia. Other agents such as diazoxide and octreotide should be reserved for refractory hypoglycemia cases in consultation with an endocrinology specialist.

43.3 Diabetic Ketoacidosis (DKA)

43.3.1 Pathophysiology

Management of diabetic ketoacidosis involves restoration of intravascular volume, correction of the insulinopenic state, and correction of metabolic derangements.

Diabetic ketoacidosis occurs as a result of insulin deficiency with rapid mobilization of energy from stores such as liver, muscle, and fat. There is an increased flux of amino acids to the liver for conversion into glucose and of fatty acids for conversion into ketones (acetoacetate, beta hydroxybutyrate, and acetone). In addition to the insulin deficiency, there is a concurrent increase in counter-regulatory hormones (i.e., epinephrine, cortisol, growth hormone, and glucagon). Such hormonal changes ultimately lead to increased glucose production and decreased peripheral glucose utilization. Hyperglycemia leads to an osmotic diuresis, depletion of intravascular volume, decreased renal blood flow, and, therefore, decreased renal glucose excretion. A decrease in renal blood flow leads to a worsening of hyperglycemia and electrolyte disturbances (total body potassium and magnesium depletion, and hypophosphatemia). Ketoacids continue to be produced and hypoperfusion leads to an increase in lactic acid. All of these findings ultimately lead to the constellation of metabolic derangements seen in DKA, namely hyperglycemia, ketonemia, and a wide anion gap acidosis, and their consequences, polyuria, dehydration, deep sighing respirations (Kussmaul) without difficulty of air entry, clouding of consciousness, and ultimately coma.

43.3.2 Clinical Manifestations

Approximately 30% of children newly diagnosed with diabetes present in DKA; rates of DKA at presentation are even higher in some locations. Ketoacidosis is often the initial presentation in children younger than 5 years of age, as the diagnosis may not be suspected and symptoms may be difficult to detect. The diagnosis of diabetes is suspected based on a history of polyuria, polydipsia, nocturia, bed-wetting, and weight loss. Findings often seen at presentation in the individual with diabetic ketoacidosis are listed in Table 43.3.

43.3.3 Treatment

Although slight differences may exist in treatment protocols, the ultimate goal in the treatment of DKA involves restoration of intravascular volume, correc-

Table 43.3 Clinical presentation of diabetic ketoacidosis

Severe dehydration
Deep respirations (Kussmaul breathing)
Depressed sensorium
Ketotic "fruity" breath
Abdominal pain
Increased or decreased blood pressure
Tachycardia

tion of metabolic derangements, and correction of the insulin deficient state with suppression of counterregulatory hormone secretion, and hence glucose production and ketogenesis. Glucose utilization is facilitated by insulin while fluid expansion enhances renal clearance of glucose as well as assisting in correction of acidosis. Figure 43.2 provides an algorithm for the management of DKA in children. During the treatment course, it is essential to keep an updated flow sheet to record chronologically the amount of fluid administered, urine output, amount of insulin administered, electrolyte values, blood gas results, blood glucose concentration, and serum osmolarity.

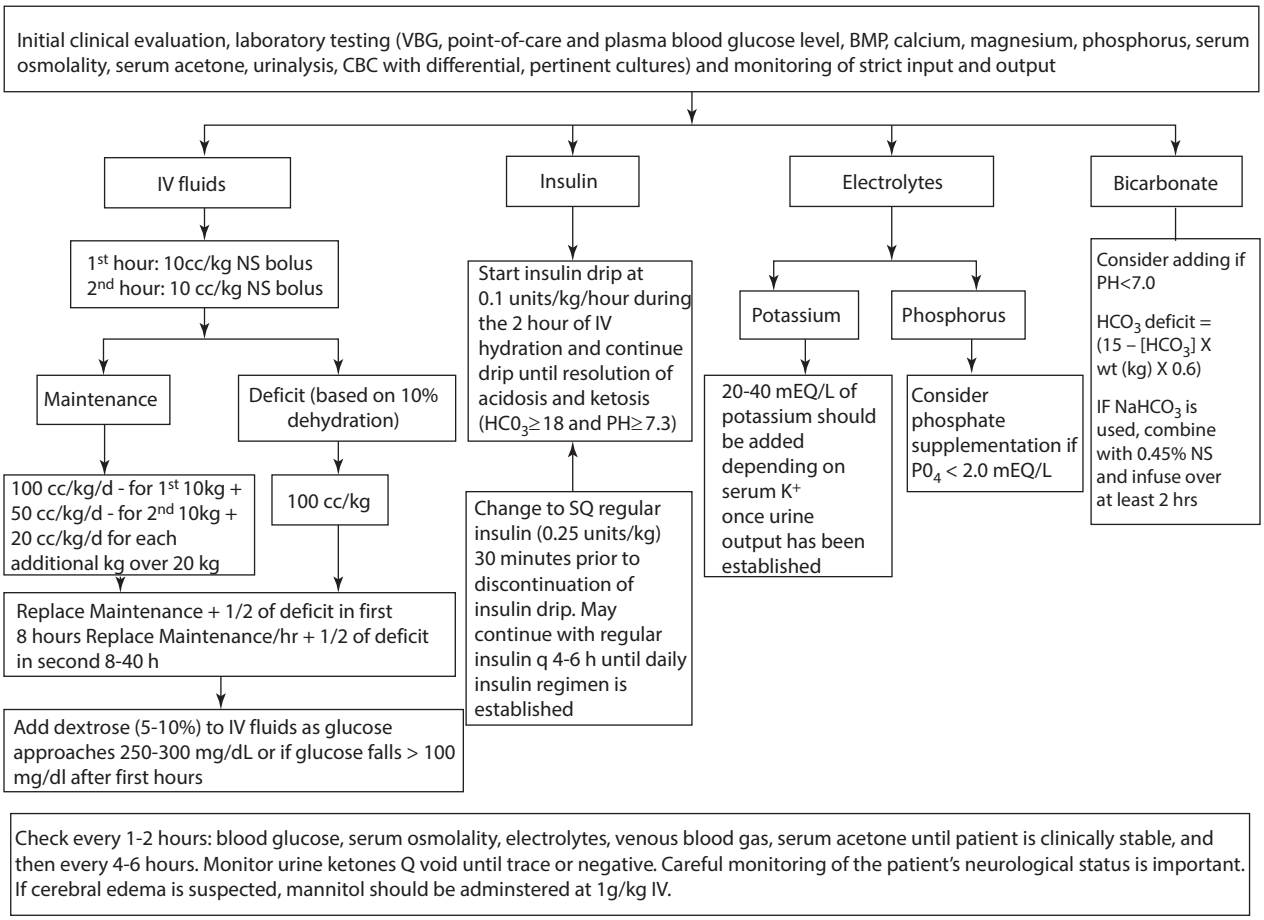
Most patients with DKA recover spontaneously with standard therapy. Over the years, the use of alkali therapy has been controversial as it may lead to a worsening of baseline metabolic derangements. Paradoxical cerebral acidosis occurs when rapidly administered HCO_3^- combines with H^+, which then dissociates to form CO_2 and H_2O. Whereas bicarbonate traverses the blood-brain barrier slowly, CO_2 diffuses rapidly thereby exacerbating cerebral acidosis. Similar physiology occurs across cell membranes leading to worsening intracellular acidosis with rapid bicarbonate administration. Rapid and early correction of acidosis with sodium bicarbonate may also worsen hypokalemia. Therefore, the administration of bicarbonate is recommended only in the most severe cases of acidosis (pH < 7.0).

The use of large amounts of chloride-containing fluids, including the chloride in potassium chloride, may result in hyperchloremia. This hyperchloremia may lead to a persistent base deficit from a low bicarbonate concentration (hyperchloremic metabolic acidosis), which may be mistaken for ongoing ketosis, but is characterized by a normal rather than increased anion gap. In these cases, measuring a serum beta-hydroxybutyrate level helps determine if ketoacidosis has resolved. Non-chloride-containing fluids such as potassium acetate or phosphate instead of potassium chloride may be useful in such cases.

Standard therapy for DKA consists of appropriate fluid composition and rate of delivery plus intravenous insulin (see Fig. 43.2 for dose) with the aim of correction of dehydration over 36–48 h rather than 24 h. For patients with uncomplicated DKA in whom peripheral circulation is not impaired, the use of subcutaneous rapid acting insulins (lispro, aspart) at an initial dose of 0.3 U/kg followed by 0.1–0.2 U/kg every 2–3 h is an acceptable alternative.

43.3.4 Morbidities

Although the mortality rate for diabetic ketoacidosis in developed countries remains low (0.15%), there continues to be considerable morbidity (Table 43.4). Metabolic derangements such as hypokalemia may trigger



Venous blood gas (VBG), Basic Metabolic Panel (BMP), Normal Saline (NS), Day (d)

Fig. 43.2 Management of diabetic ketoacidosis in children. Volume repletion, insulin therapy, electrolyte replacement, and bicarbonate therapy

dangerous cardiac arrhythmias, while hyperkalemia may lead to cardiac arrest. Serum phosphorus levels often decline during DKA treatment resulting in hypophosphatemia. Most DKA protocols include IV phosphorus replacement with at least 20 mmol/L of KPhosp. Severe dehydration can lead to vascular thrombosis. An underlying infection may go unrecognized and result in sepsis. Treatment may also be associated with complications.

Given the hyperglycemia and associated hyperosmolality seen in patients with DKA, normal saline (0.9%) is recommended as the initial hydrating fluid. A gradual decline in osmolality is desired, as rapid changes in osmolality have been implicated in cerebral edema, which is said to account for the majority of all DKA deaths. Although rapid osmotic changes are thought to cause cerebral edema and brain injury in DKA, more recent data using MRI scans suggests that the edema is often vasogenic rather than cytotoxic. In addition, some data suggest that brain blood flow is increased in brain regions supplied by the anterior and middle cerebral arteries, whereas blood flow is reduced in the posterior cerebral artery circulation (brainstem and occipital lobe). Vasogenic edema may represent the effects of ischemia followed by reperfusion during treatment leading to capillary leak at the blood-brain barrier. A large multicenter trial compared the outcome of children randomized in a 2 × 2 factorial designed trial to rapid versus slow (presumed 10% dehydration versus 5%

Table 43.4 Complications of diabetic ketoacidosis

Cerebral edema	Acute respiratory distress syndrome
Hypokalemia and arrhythmias	Hypoglycemia from insulin treatment
Hyperkalemia and cardiac arrest	Unrecognized underlying infection
Vascular thrombosis Hypophosphatemia causing muscle weakness and altered mental status	

dehydration) rehydration and use of normal saline versus 0.45% saline. There was no difference in the incidence of Glasgow Coma Scores <14 or clinically apparent brain injury between the two groups. The results of this trial support the suggestion that mechanisms other than just an osmotic etiology of brain injury should be considered.

Factors associated with an increased risk of cerebral edema include severity of acidosis at presentation, treatment with bicarbonate, high urea nitrogen, an attenuated rise in serum sodium as the glucose concentration falls, and possibly excessive rate of fluid administration.

Factors associated with an increased risk of cerebral edema include treatment with bicarbonate, attenuated rise in serum sodium concentration as glucose concentration declines, high serum urea nitrogen at presentation, excessive rate of fluid administration, severity of acidosis at presentation, and young age. Those with a lower blood pressure at presentation and higher blood pressure during hospitalization for DKA were also more likely to develop cerebral edema in a large retrospective cohort of 1225 children at the Children's Hospital of Pittsburgh. Since sodium is the major determinant of serum osmolality, sodium concentration should rise as the osmolality contribution from the high glucose concentration falls. This assures that the serum osmolality will not decline too rapidly. New onset diabetes, especially in those less than 5 years of age, is also associated with an increased risk for developing cerebral edema, perhaps because the duration of undiagnosed disease has been longer, and hence clinical and biochemical derangements are more severe at the time of diagnosis.

Cerebral edema usually occurs in the first 4–12 h of treatment but may be present prior to treatment and may occur anytime during treatment.

Early recognition of the patient with suspected cerebral edema is crucial. Cerebral edema typically occurs 4–12 h after treatment is started but may be present prior to treatment or may develop anytime during treatment. Warning signs include headaches, bradycardia, recurrence of vomiting, change in neurological status (restlessness, irritability or drowsiness), rise in blood pressure, or a decrease in oxygen saturation. A rapid or ongoing rise in serum sodium concentration may represent a late adverse effect from possible cerebral edema as a result of free water loss in the urine from diabetes insipidus. When cerebral edema is suspected, the rate of fluid administration should be reduced, and mannitol should be administered (0.5–1 g/kg IV) over 30 min. If there is no response to mannitol, 3% NaCl (2.5–5 mL/kg) over 15–30 min may also be used. Although hypertonic saline is used more frequently for the treatment of cerebral edema from trauma and other conditions in the ICU, an analysis of a large administrative database observed a significant increase in risk-adjusted mortality associated with the use of 3% NaCl rather than mannitol. This does not prove causation but suggests caution until further data are available. It is important to perform frequent neurological assessments and close observation in an intensive care unit setting. Once the patient is stable, a CT or MRI can be performed to confirm the diagnosis, although the value of imaging in these children has been questioned, as obtaining a CT scan may delay hyperosmolar treatment.

Although cellular edema from osmotic shifts was thought to be the main mechanism for cerebral edema, more recent data suggest that inflammation and ischemia-reperfusion lead to vasogenic edema in DKA.

Warning signs suggestive of cerebral edema include headaches, bradycardia, recurrence of vomiting, change in neurologic status, rise in blood pressure, or a decrease in oxygen saturation.

A rapid ongoing rise in serum sodium may be indicative of diabetes insipidus resulting from severe cerebral edema.

43.4 Hyperglycemic Hyperosmolar State (HHS)

43.4.1 Pathophysiology

HHS occurs when the glucose concentration is extremely elevated, often exceeding 600 mg/dL with an effective osmolality of >300 mosm/L in the absence of ketosis since these children have moderate insulin deficiency which impairs glucose uptake but suppresses lipolysis and ketosis. A recent study observed that 2% of children with Type 2 diabetes may present with HHS. There is often profound dehydration and loss of electrolytes at the time of presentation secondary to a prolonged prodromal period and lack of the typical symptoms associated with DKA (vomiting, hyperventilation).

43.4.2 Clinical Manifestations

Signs of dehydration with HHS may be less apparent because intravascular volume is preserved from the high plasma glucose concentration leading to hypertonicity. There is often a pronounced osmotic diuresis that may last for hours in those with very high plasma glucose concentrations.

43.4.3 Morbidities

Complications of HHS are similar to those complications seen in DKA. However, with HHS, there is a greater risk of venous thrombosis, pulmonary emboli, pulmonary edema, cerebral edema, severe hypophosphatemia, rhabdomyolysis, malignant hyperthermia, and acute renal injury or renal failure.

43.4.4 Treatment

More aggressive replacement of intravascular volume is often needed to effectively treat HHS. An initial 20 cc/kg fluid bolus using normal saline (0.9%) followed by ½ normal saline (0.45%) or ¾ normal saline over 24–48 h can be used to replace fluid losses with the goal of gradually correcting serum sodium concentration and serum osmolality. Given the profound diuresis typically seen with HHS, it is often necessary to replace urinary losses with NaCl (0.45% or 0.9%), and it is important to monitor for electrolyte deficits frequently (q2–3 h). With HHS, insulin does not have to be added until the blood sugar stabilizes with IV fluids alone since endogenous insulin concentrations are higher than seen with DKA. However, insulin can be initiated sooner in those patients who present with severe acidosis and ketosis at 0.025–0.05 U/kg/h with the goal of decreasing plasma glucose by 50–75 mg/dL/h (3–4 mmol/h). A relatively slow reduction in the glucose concentration and serum osmolality is desired to reduce the risk of cerebral edema.

43.5 Pheochromocytoma

Classical symptoms of pheochromocytoma include episodic or sustained hypertension, sweating, headache, blurred vision, anorexia, and vomiting.

43.5.1 Clinical Presentation

The clinical presentation of pheochromocytoma is variable with some patients remaining asymptomatic for years. Classical symptoms include episodic or sustained hypertension, sweating, headache, blurred vision, anorexia, and

vomiting. In children with hypertension, the prevalence of pheochromocytoma is approximately 1.7%.

43.5.2 Diagnosis

The diagnosis of pheochromocytoma is made by documenting elevated plasma and/or urinary catecholamines and metabolites.

The diagnosis of pheochromocytoma is made by documenting increased catecholamine secretion. This can be accomplished by measuring plasma free metanephrines (with patient in a supine position) or urinary fractionated metanephrines. Certain medications may affect plasma or urine metanephrine levels, including acetaminophen, mesalamine, sulfasalazine, buspirone, β-blockers, or tricyclic antidepressants. The use of age-appropriate reference ranges of metanephrine and catecholamine concentrations for detection of childhood pheochromocytomas has been proposed (Table 43.5).

Imaging studies such as computed tomography and magnetic resonance imaging are very useful in localizing pheochromocytomas. With suspected metastatic disease, scintigraphy with radiolabeled metaiodobenzylguanidine (I^{123} MIBG) or ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT scanning can be used to determine the extent of extra-adrenal multifocal or recurrent disease.

43.5.3 Treatment

Preoperative management of the patient with a pheochromocytoma includes hydration with intravenous fluids, continuous EKG monitoring, and selective alpha-adrenergic blockade.

Surgery is the treatment of choice for pheochromocytomas. Perioperative mortality of patients with pheochromocytoma has dropped to less than 3% since the introduction of alpha-adrenergic blocking drugs. Preoperative manage-

Table 43.5 Biochemical values in healthy boys and girls and in pediatric patients with or without pheochromocytoma

	Reference groups		Patients with confirmed tumor
	Boys	Girls	
Plasma (pmol/mL with 95% confidence intervals)			
Normetanephrine	0.26 (0.11–0.530)	0.21 (0.11–0.42)	3.19 (1.41–9.06)
Metanephrine	0.20 (0.08–0.52)	0.15 (0.06–0.37)	0.17 (0.01–0.24)
Norepinephrine	1.04 (0.53–2.02)	1.03 (0.57–1.91)	8.60 (1.84–33.39)
Epinephrine	0.16 (0.05–0.59)	0.11 (0.03–0.46)	0.10 (0.03–0.43)
24 h urine (μmol/24 h with 95% confidence intervals)			
Normetanephrine	0.98 (0.49–1.78)	0.69 (0.35–1.56)	6.69 (4.84–23.49)
Metanephrine	0.52 (0.24–1.01)	0.32 (0.15–0.85)	0.30 (0.22–0.53)
Norepinephrine	0.15 (0.08–0.29)	0.12 (0.06–0.25)	1.48 (0.58–5.56)
Epinephrine	0.02 (0.01–0.06)	0.01 (0–0.04)	0.03 (0–0.05)

Data from Weise et al. (2002)

ment includes initiation of a high sodium diet, hydration with intravenous fluids, continuous electrocardiogram monitoring, and alpha-adrenergic blockade. Alpha-adrenergic drugs can be initiated 1–2 weeks before planned surgery to normalize blood pressure and heart rate. Calcium channel blockers and β-blockers can be used in addition to alpha-adrenergic blockers in patients with persistent tachycardia or arrhythmias. Iobenguane I 131 (Azedra™), a radioactive systemic agent administered by intravenous injection, was FDA approved in 2018 for the treatment of locally advanced, unresectable pheochromocytomas, paragangliomas, or metastatic disease in adults and adolescents (>12 years old) who need systemic therapy. Iobenguane I 131 was found to decrease the need for antihypertensive drugs while shrinking tumor size.

Pheochromocytomas may be found in isolation or in association with other tumors as is common in conditions such as multiple endocrine neoplasia 2 (MEN2) caused by a mutation in the RET gene, von Hippel-Lindau disease (VHL) caused by a mutation in the VHL tumor suppressor gene, and neurofibromatosis type I (NF-1). Molecular identification of a mutation in any of these genes is important in disease surveillance, early diagnosis of tumors, and more effective treatment before onset of clinical disease. For patients with MEN-2B who may have coexistent pheochromocytoma and medullary carcinoma of the thyroid, it is important to remove the pheochromocytoma first to diminish the risk of a severe hypertensive episode which could occur while operating on the thyroid gland. Because these entities are often familial, discovery in a child should alert the physician to screen other close family members for these tumors.

Despite improved preoperative management, patients with pheochromocytomas are still at high-risk during anesthetic induction and intubation, during tumor manipulation, and following ligation of the tumor's venous drainage when hypotension often occurs. Careful monitoring and intravenous hydration are critical during surgery and in the postoperative period. Patients undergoing partial or bilateral adrenalectomy need to be monitored for the onset of adrenal insufficiency.

43.6 Adrenal Insufficiency

43.6.1 Clinical Presentation

An acute adrenal crisis usually occurs in the child with undiagnosed chronic adrenal insufficiency who is subjected to stress such as a major illness, trauma, or surgery. Many conditions can cause adrenal insufficiency (◘ Tables 43.6 and 43.7), including acute critical illness, also called critical illness-related cortisol insufficiency (CIRCI). The major presenting symptoms and signs are listed in ◘ Table 43.8.

Laboratory findings suggestive of acute adrenal insufficiency include hyponatremia, hypochloremia, hyperkalemia, metabolic acidosis, and hypoglycemia.

43.6.2 Diagnosis

The definitive diagnosis of adrenal insufficiency is made by demonstrating an inappropriately low serum cortisol in the context of an acute illness or injury. The variability in criteria used to diagnosis adrenal insufficiency has made interpretation of results challenging. The greatest controversy has been defin-

Table 43.6 Primary causes of adrenal insufficiency

Congenital adrenal hyperplasia
Sepsis/infections
Autoimmune polyglandular syndrome
Addison's disease
Adrenal hemorrhage
Adrenoleukodystrophy
Congenital adrenal hypoplasia ACTH resistance syndromes Triple A-Allgrove syndrome IMAGe syndrome

Table 43.7 Secondary causes of adrenal insufficiency

Glucocorticoid withdrawal
Hypopituitarism
Hypothalamic tumors
CNS irradiation
Medication-induced (e.g., fluconazole, dopamine, etomidate) Acute critical illness (critical illness-related cortisol insufficiency (CIRCI))

Table 43.8 Clinical presentation of adrenal crisis

Abdominal pain	Nausea
Fever	Vomiting
Seizures	Anorexia
Weakness	Hypotension
Apathy	

ing the threshold cortisol concentration for the adrenal stress response to be deemed acceptable and below which value a patient should be considered to have adrenal insufficiency and be treated.

Several studies using different diagnostic criteria investigated the incidence of adrenal insufficiency in critically ill patients. The incidence of adrenal insufficiency in children with sepsis or septic shock ranged from 17% to 88% depending on the diagnostic criteria used. Determining the presence of CIRCI (also called acute adrenal insufficiency) is complicated by the lack of a standard assay that accounts for the high binding of cortisol (~90–95%) to a cortisol-binding globulin and to a lesser extent (~5%) albumin; the concentration of both proteins are often depressed in critically ill children. In addition, although an early morning cortisol represents the peak in humans, the cortisol diurnal variation may be lost so that a random level is often obtained. Furthermore, multiple critical illness induced endocrine dysfunctions may be present, depending on the thresholds used to diagnose endocrine disorders.

Table 43.9 Diagnostic criteria, dose of ACTH used for adrenal stimulation, and incidence of adrenal insufficiency in children with septic shock

Authors	Diagnostic criteria	ACTH dose used	Incidence of Adrenal Insufficiency
Hatheril et al.	Peak cortisol increase <7 μg/dL	145 μg/m^2	52%
Menon et al.	Basal cortisol <7 μg/dL	125 μg (weight <10 kg)	31%
	Peak cortisol <18 μg/dL	250 μg (weight > 10 kg)	
Bone et al.	AM basal cortisol <5 μg/dL	0.5 μg/m^2	17%
	Peak cortisol <18 μg/dL		
Hebbar et al.	Basal cortisol < 18 μg/dL	1 mcg	88%
Karagüzel et al.	Δ cortisol <9 μg/dL	1 mcg	17%

ACTH adrenocorticotropin hormone. Peak cortisol is cortisol concentration after administration of ACTH

A baseline cortisol concentration < 5 μg/dL during a period of stress with failure of the cortisol concentration to rise above 18 μg/dL 30 min after IV cosyntropin is highly suggestive of adrenal insufficiency and should be treated.

A summary of these studies, including the diagnostic criteria, dose of ACTH, and incidence of adrenal insufficiency is provided in Table 43.9.

The standard ACTH stimulation test is performed using IV or intramuscular synthetic ACTH (cosyntropin) at a dose of 15 μg/kg in infants, 125 μg in younger children (<2 years of age), or 250 μg in older children (>2 years of age) with measurements of cortisol levels at baseline and at 30 and 60 min following the administration of ACTH. More recent studies used a smaller dose (1 μg) of ACTH, which was found to have a high sensitivity and specificity in identifying patients with adrenal insufficiency or in assessing adrenal recovery from glucocorticoid suppression. Most would agree that a baseline cortisol level of less than 5 μg/dL during a period of stress and failure of cortisol to rise to more than 18 μg/dL 30 min after IV cosyntropin is consistent with adrenal insufficiency and should be treated as such. Note that a patient with head trauma or other brain injury causing secondary adrenal insufficiency may have an appropriate cortisol response to ACTH bolus stimulation since the cause of secondary adrenal insufficiency was pituitary ACTH deficiency. If the cortisol concentration is less than 5 μg/dL, an elevated ACTH level (>twofold the upper limit of the reference range) is consistent with primary adrenal insufficiency, while a low ACTH level (i.e., <10 pg/mL) is suggestive of secondary adrenal insufficiency. Plasma renin and aldosterone can also be measured simultaneously to determine the presence of mineralocorticoid deficiency.

The insulin tolerance test has also proven to be a valuable test in assessing the hypothalamic-pituitary-adrenal axis. When performed by an experienced clinician under close supervision, complications related to hypoglycemia can be minimized and important diagnostic information can be obtained. Other pharmacological stimuli may also be used in the critically ill child to assess for growth hormone deficiency, including clonidine (5 mcg/kg), arginine (0.5 g/kg IV over 30 min), and/or glucagon (0.03 mg/kg) subcutaneously.

As with most endocrine/metabolic disorders, obtaining a blood sample prior to the initiation of treatment is critical as interpretation of laboratory data after the onset of treatment can be misleading and may delay diagnosis.

43.6.3 Treatment

Strong evidence for a positive effect of glucocorticoid treatment on mortality in critically ill children with critical illness related corticosteroid insufficiency is still lacking with unresolved questions regarding the timing and continuation or discontinuation of treatment. Clinically, children with acute adrenal insufficiency may have poor responsiveness to catecholamine infusions to support their blood pressure and perfusion since corticosteroids are important for β-adrenergic receptor expression and function. Thus, it is not surprising that most studies using stress-dose hydrocortisone show short-term improvement in cardiovascular status with a reduction in vasoactive drug support; however, the studies have not shown long-term benefit on outcome.

Patients with known adrenal insufficiency should be on daily maintenance hydrocortisone (8–12 mg/m^2/day). Hydrocortisone is the drug of choice because it represents the major glucocorticoid secreted physiologically by the adrenal glands. The goal of maintenance therapy in children is to treat the adrenal insufficiency while ensuring normal growth velocity and minimizing the side effects associated with long-term glucocorticoid treatment. In children with primary adrenal insufficiency and coexisting aldosterone deficiency, fludrocortisone at a starting dose of 100 μg/day should be added.

Patients in the ICU are under considerable stress whether they are recovering from surgery or from a major illness. The individual with a history of chronic steroid use (more than a few weeks) is at particularly high risk for adrenal crisis with abrupt discontinuation of steroids or if maintenance doses of steroids are not increased during an acute illness.

Antifungal agents such as fluconazole and ketoconazole, two agents often used in the ICU for the treatment of systemic candida infections, have been shown to cause acute adrenal insufficiency when used in high doses. Recent studies suggest that a single dose of etomidate may increase the risk for adrenal insufficiency during pediatric critical illness. Regardless of the cause, those with adrenal insufficiency are unable to mount an appropriate response in the context of major stress and, therefore, should be placed on double to triple their maintenance steroid dose to prevent an adrenal crisis. This can be accomplished orally with hydrocortisone, via intramuscular (IM) injection with hydrocortisone (Solucortef) or with an intravenous bolus of 25–50 mg/m^2 of hydrocortisone for acute management followed by 50 mg/m^2/day divided Q6H, or as a continuous infusion along with dextrose containing intravenous fluids. Once the patient is clinically stable, maintenance therapy can be resumed.

An intravenous bolus of 25–50 mg/m^2 of hydrocortisone can be used for the acute management of adrenal insufficiency followed by 50 mg/m^2/day divided Q6H or as a continuous infusion along with dextrose containing intravenous fluids.

43.7 Congenital Adrenal Hyperplasia

43.7.1 Presentation

Congenital adrenal hyperplasia (CAH) results from inherited defects in one of the five enzymatic steps required for the biosynthesis of cortisol from cholesterol. Although CAH can be viewed as a spectrum of disorders, it is usually divided into two broad categories: classical (severe, salt-wasting) and nonclassical (nonsalt-losing or simple virilizing) CAH. The most frequent cause of

classical CAH is a deficiency in 21-hydroxylase, an enzyme important in the synthesis of glucocorticoids and mineralocorticoids. Females affected by the disorder are usually identified early in the prenatal or postnatal period because of the presence of ambiguous genitalia with clitoromegaly (with or without labial fusion) and hyperpigmentation of the genitalia and skin creases. With the initiation of newborn screening for CAH, male infants, who often have no overt findings to suggest androgen excess, can now be diagnosed early and treated prior to succumbing to life-threatening hyponatremia, dehydration, and shock.

It is important to distinguish CAH from nonadrenal conditions such as salt-losing nephropathy or posterior urethral valves in male infants, which may have similar biochemical findings (hyponatremia, hyperkalemia).

43.7.2 Laboratory Findings

Biochemical findings in patients with classical CAH include hyponatremia, hyperkalemia, metabolic acidosis, a markedly elevated 17-hydroxyprogesterone (>2000 ng/dL after 24 h of age), and elevated androstenedione and testosterone levels. An elevated renin level is indicative of salt wasting.

43.7.3 Treatment

Treatment of congenital adrenal hyperplasia includes maintenance hydrocortisone (10–15 mg/m^2/day), mineralocorticoid replacement, and salt supplementation.

Usual treatment for CAH includes hydrocortisone given at a dose of 10–15 mg/m^2/day divided into two to three daily doses. Mineralocorticoid replacement with oral fludrocortisone acetate (Florinef) at a dose of 0.1 mg daily is also required.

Sodium chloride supplementation (2–3 g/day) is recommended in infants and children to maintain plasma sodium concentration and renin in the normal range. During times of stress, patients are instructed to double or triple the maintenance dose. Intravenous saline (0.45–0.9% NaCl) plus 5% glucose containing fluids and intravenous hydrocortisone at 50–100 mg/m^2/day divided every 6–8 h or as a continuous infusion should be given during an acute salt-losing crisis.

Glucocorticoid dose should be doubled or tripled during times of acute illness (e.g., high fever or vomiting) or prior to surgery.

Patients with classical CAH cannot mount a sufficient cortisol response to physical stress and require additional doses of hydrocortisone in situations such as febrile illnesses, surgery, and significant trauma. Patients with CAH should be instructed that hydrocortisone doses should be increased perioperatively for major surgery accompanied by general anesthesia. Some clinicians still recommend high dose steroids the day prior to a major surgery but many now restrict use to induction of anesthesia. Intravenous hydrocortisone can be administered via a continuous infusion (50–100 mg/m^2/day) or in four divided doses during the procedure and postoperatively until the patient is able to tolerate oral medications, after which time, they should be given three times the oral maintenance dose for the next 24 h.

43.8 Thyroid Abnormalities

43.8.1 Normal Actions of Thyroid Hormone

Thyroid hormones, T4 (thyroxine) and T3 (triiodothyronine) circulate bound to thyroid binding proteins (TBPs). Free hormone is transported into the thy-

roid cell by specific transport systems. Thyroxine is converted to T3 by 5′ deiodinase (outer-ring deiodination) within the cytoplasm. In the nucleus, T3 binds to its receptor, which in turn binds to specific thyroid hormone response elements (TREs) on DNA where transcription of specific thyroid hormone responsive genes is initiated.

Thyroid hormone has a number of physiologic effects. In the prenatal and postnatal periods, thyroid hormone plays a major role in brain development and skeletal maturation. It is important in regulating a number of homeostatic processes including energy and heat production. It has effects on lipid and carbohydrate metabolism. Thyroid hormone also stimulates the transcription of genes important in the regulation of cardiac contractility.

43.8.2 Acute Hyperthyroidism

Thyroid hormone increases the expression and responsiveness of beta-adrenergic receptors, which explains the characteristic pathophysiological and clinical manifestations of both hyper- and hypothyroidism.

Thyrotoxicosis is an uncommon disorder of childhood resulting from thyroid follicular cell hyperfunction secondary to TSH-stimulating immunoglobulins with increased synthesis of T4 and T3. Most patients with Graves' disease present with classic symptoms and signs (Table 43.10), which prompt further laboratory investigation. Free thyroxine (free T4) values are elevated while thyroid-stimulating hormone (TSH) values are suppressed. Acute hyperthyroidism can also be seen with thyroid follicular cell destruction as is seen in Hashitoxicosis, or subacute thyroiditis (de Quervain's thyroiditis). It can also be caused by ingestion of thyroid hormone or other iodide preparations. Less common causes of hyperthyroidism are TSH secreting tumors, such as pituitary or ectopic tumors. Other conditions associated with hyperthyroidism are listed in Table 43.11.

43.8.3 Treatment

Antithyroid drug therapy remains the treatment of choice in children less than 10 years of age. Methimazole and propylthiouracil (PTU) were the two drugs used for long-term therapy of children in the United States. However, in 2008 an expert panel evaluated the safety of PTU in children and found there was a significantly increased risk of severe PTU-induced liver failure in 1:2000–

Table 43.10 Clinical presentation of acute hyperthyroidism

Nervousness and irritability	Heat intolerance
Palpitations and tachycardia	Sleep disturbances
Tremor	Changes in vision, photophobia, diplopia
Weight loss	Exophthalmos
Alterations in appetite	Thyroid enlargement
Frequent bowel movements	Weakness
Menstrual disturbance	

Table 43.11 Causes of acute hyperthyroidism

Toxic diffuse goiter (Graves' disease)
Hashitoxicosis
Toxic adenoma
Toxic multinodular goiter
Painful subacute thyroiditis (de Quervain's thyroiditis)
Excessive ingestion of thyroid hormone
Silent thyroiditis (i.e., postpartum and lymphocytic) Activating mutation in the TSH receptor resulting in neonatal thyrotoxicosis in the absence of maternal TSH-stimulating antibodies that crossed the placenta

Table 43.12 Common medications used to treat hyperthyroidism in children

	Dose
I. Antithyroid drugs (mg/kg/day)	
Methimazole	0.4–0.6 divided QD-BID (TID)
Carbimazole	0.4–0.6 divided QD-BID
II. Beta-adrenergic blockers	
Atenolol	25–50 mg QD-BID
Propranolol	10–20 mg TID-QID

1:4000 children. As a result of this finding, the panel recommended discontinuing the use of PTU in children in favor of alternate therapies. Methimazole is not associated with a risk of liver failure in children. It can also be used once daily, which results in better compliance, and patients taking methimazole often have more rapid improvement in serum concentration of thyroxine and triiodothyronine. Neither medication blocks the release of stored thyroid hormone into the circulation. Therefore, most patients require treatment for 4–8 weeks before a euthyroid state can be reached. A saturated solution of potassium iodide (SSKI) can be used in severe cases of hyperthyroidism and is effective in inhibiting the release of preformed thyroid hormone. Dosing regimens of medications used to treat hyperthyroidism in children is provided in Table 43.12.

Beta-adrenergic blockers are often used as adjunctive therapy to alleviate the hyperadrenergic symptoms that occur during the thyrotoxic course of the disease. Although still controversial, the use of radioactive iodine therapy in the treatment of children with Graves' disease is gaining more acceptance with several studies showing a clear benefit with minimal to no long-term side effects. Given the high relapse rate and potential side effects of antithyroid medication, more clinicians are advocating the use of radioactive iodine therapy as first-line therapy in adolescents with mild to moderate hyperthyroidism.

Finally, either subtotal or total thyroidectomy can be performed in children who develop a hypersensitivity reaction to antithyroid medications, are refractory to medical treatment, are unable to tolerate antithyroid medication, or in those for whom a solid nodule is present, thereby raising the suspicion of thy-

roid carcinoma. However, such procedure is not without complications such as removal or infarction of parathyroid glands, or injury to the recurrent laryngeal nerve; therefore, surgery should only be performed by a surgeon with sufficient experience in pediatric thyroid surgery. When surgery is performed for thyrotoxicosis or resection of a thyroid tumor, careful monitoring of serum calcium levels postoperatively is mandatory because of the possibility of postsurgical hypoparathyroidism, which may be temporary or permanent.

43.8.4 Hypothyroidism

Hypothyroidism in infants and young children results in marked slowing of growth and development with serious consequences including mental retardation. In the older child or adolescent, one may elicit a history of weight gain, dry skin, cold intolerance, constipation, coarseness of hair, and/or fatigue and delayed puberty/menarche. There have also been several reports of multiple ovarian cysts in association with hypothyroidism, possibly due to VanWyk-Grumbach syndrome which postulates that high TSH concentrations may interact with the FSH receptor due to structural similarity between FSH and TSH. An enlarged, firm thyroid gland is usually present on examination.

Complications of hypothyroidism in the older child or adolescent are very rare. Because patients with myxedema absorb drugs poorly, levothyroxine should be administered intravenously while the patient is in the intensive care unit. In general, caution should be taken when administering medications to hypothyroid individuals, as they have a decreased metabolic clearance, which may prolong the drugs' effect.

As hypothyroidism and adrenal insufficiency may coexist, a morning cortisol level should be measured. In patients found to be adrenal insufficient, hydrocortisone should be replaced prior to thyroid hormone replacement so as not to precipitate an adrenal crisis (as thyroid hormone may increase the metabolic clearance of cortisol and increase metabolic rates).

43.8.5 Nonthyroidal Illness

Acute or chronic illness may have profound effects on circulating levels of thyroid hormone. Such adaptation may represent a protective mechanism used by organisms during times of severe illness.

Activation of 5′-deoidinase accelerates conversion of T4 to reverse T3 (rT3; inner-ring deiodination). An elevation in cytokines such as tumor necrosis factor inhibits type 1 5′-deoidinase, decreasing T3 production. In this setting, serum T3 and T4 levels are both low, which is characteristic of the euthyroid sick syndrome. As the severity of the nonthyroidal illness worsens, rT3 rises while free T4 and total T4 levels fall. Thyroid-stimulating hormone (TSH) is usually normal provided the patient is not receiving dopamine, corticosteroids, or amiodarone, which are agents known to reduce thyroid hormone levels.

In children undergoing cardiac surgery, the degree of thyroid hormone abnormality consistent with the euthyroid sick syndrome correlated with the severity of illness, higher need for inotropic support, duration of mechanical ventilation, and length of cardiac ICU stay.

Table 43.13 outlines the major differences in diagnosis and treatment between patients with acquired or congenital hypothyroidism and euthyroid sick syndrome.

Medications such as dopamine, corticosteroids, or amiodarone can affect thyroid hormone levels.

Table 43.13 Key differences between hypothyroidism and euthyroid sick syndrome

	Etiology	Laboratory findings	Treatment
Hypothyroidism	Congenital	Elevated TSH, low T4, and free T4	Levothyroxine daily
	Acquired (primary)	Elevated TSH, low T4, and free T4 + thyroid peroxidase and thyroglobulin antibodies	Levothyroxine daily
	Acquired (secondary)	Low TSH, low T4, and free T4	Levothyroxine daily
Euthyroid sick syndrome	Severe acute illness (DKA, trauma, burns, febrile states cirrhosis, renal failure)	Low T3 and free T3	Treat underlying illness
		Low T4	
		Normal to low free T4	
		Normal TSH	
		Increased or normal rT3	
	Medication induced (PTU, propranolol, dexamethasone, amiodarone, contrast agents, dopamine)	Low T3 and free T3	Discontinuation of medication if possible
		Normal, low, or high T4	
		Normal to low free T4	
		Normal to high TSH	
		Low TSH (dopamine[a])	
		Increased or normal rT3	

ESS euthyroid sick syndrome, *PTU* propylthiouracil, *TSH* thyroid-stimulating hormone, *DKA* diabetic ketoacidosis

[a]Dopamine potently suppresses TRH-stimulated TSH release; so TSH levels are low and a TRH-stimulation test cannot be interpreted in a patient receiving a dopamine infusion

The thyroid hormonal abnormalities seen in nonthyroidal illness usually normalize once the patient recovers. Therefore, treatment for biochemical hypothyroidism in the setting of severe illness is usually not necessary as patients can be reevaluated once their clinical status has improved. Nevertheless, there have been isolated reports of a reduced need for ionotropic support in patients with presumed euthyroid sick syndrome treated with thyroid hormone replacement, especially following cardiac surgery.

Reduced T3 has been implicated in the progressive loss of cardiac contractility after brain stem death. Infusions of T3 have, therefore, been recommended in brain dead individuals for preservation of donor hearts prior to transplantation.

43.9 Calcium Homeostasis and Regulation of Extracellular Calcium

Serum calcium concentration is maintained mostly by dietary intake and absorption from the intestinal tract (mediated by 1, 25 dihydroxyvitamin D_3), and by mobilization of calcium from bone and reabsorption across the renal tubules through the action of parathyroid hormone (PTH). Thyrocalcitonin, a peptide produced in the parafollicular (C) cells of the thyroid gland, is important in lowering the serum calcium concentration. It is secreted in response to an increase in ionized calcium concentration and acts by inhibiting calcium and phosphate reabsorption in the kidney and by suppressing resorption of bone by inhibiting osteoclast activity.

Extracellular calcium levels are tightly regulated within a narrow physiologic range, which allows for the proper functioning of many tissues: excitation-contraction coupling in muscle, synaptic transmission in the nervous system, platelet aggregation, coagulation, and secretion of hormones and other regulators by exocytosis.

Calcium plays an important role in many biological processes including excitation-contraction coupling in muscle, synaptic transmission in the nervous system, platelet aggregation, coagulation, and secretion of hormones and other regulators by exocytosis.

43.9.1 Hypocalcemia

Since about 50% of calcium is bound to albumin and critically ill patients often have low albumin concentrations, the diagnosis of hypocalcemia should be confirmed by measurement of ionized calcium concentration rather than total serum calcium concentration.

A deficiency in magnesium (required for the production and release of parathyroid hormone [PTH]), vitamin D, or PTH may result in hypocalcemia. Patients with chronic renal failure have a tendency toward phosphate retention and hypocalcemia. An increase in serum phosphate causes a decrease in calcium as the body attempts to maintain homeostasis by maintaining the calcium x phosphate product constant, so that as the phosphate concentration increases, the calcium concentration must decrease. A decrease in serum calcium concentration stimulates PTH secretion, which leads to secondary hyperparathyroidism, further exacerbating the hypocalcemia. These patients are best treated by restricting dietary phosphate intake and using phosphate-binding antacids.

Major causes of hypocalcemia and associated PTH and vitamin D levels are shown in ◘ Table 43.14. Although listed in ◘ Tables 43.14 and 43.15, calcitonin levels are not routinely measured in individuals with calcium and/or phosphate abnormalities.

◘ **Table 43.14** Causes of hypocalcemia and associated levels of PTH, vitamin D, and calcitonin

	PTH	Vitamin D	Calcitonin
Hypoparathyroidism	↓	Normal	↓
Pseudohypoparathyroidism	↑	Normal	↓
Vitamin D deficiency	↑	Low	↓
Hyperphosphatemia	↑	Low	↓
Hypomagnesemia	↓	Normal	↓

Table 43.15 Causes of hypercalcemia and associated levels of PTH, PTHrP[a], vitamin D, and calcitonin

	PTH or PTHrP	Vitamin D	Calcitonin
Hyperparathyroidism	↑	Normal	↑
Familial hypocalciuric hypercalcemia (FHH)	↑↓/Normal	Normal	↑
Hypervitaminosis D	↓	↑	↑
Immobilization	↓	Normal	↑
Neoplasia	↑ PTHrP	Normal	↑
Vitamin A intoxication	↓	Normal	-

[a]PTHrP is PTH-related peptide

Acute treatment of hypocalcemia: 30–60 mg/kg of calcium gluconate or 10–20 mg/kg of calcium chloride every 4–6 h. Magnesium should be replaced if hypomagnesemia is present.

Acute treatment of hypocalcemia consists of the IV administration of a calcium solution, usually 10% calcium gluconate (30–60 mg/kg) or 10% calcium chloride (10–20 mg/kg), which can be given every 4–6 h; the different doses deliver approximately the same mmol of elemental calcium. If hypomagnesemia is present, 25 mg/kg of magnesium sulfate may be given IV over 2 h with attention to blood pressure, or 24–48 mg/kg/day of elemental Mg^{2+} may be given orally as magnesium chloride, citrate or lactate. The long-term treatment of hypocalcemia is dependent on the etiology, but usually consists of vitamin D replacement and calcium and/or magnesium supplementation (see also ► Chap. 35).

43.9.2 Hypercalcemia

Hypercalcemia usually occurs as a result of PTH hypersecretion which may result from hyperplasia of the parathyroid glands or by an adenoma. Other causes of hypercalcemia with their associated PTH, vitamin D, and calcitonin levels are listed in Table 43.15.

Acute treatment of hypercalcemia: 1½–2 times maintenance fluids +/– furosemide.

The treatment of hypercalcemia consists of inducing a saline diuresis using generous hydration with 1½–2 times maintenance fluids (as 5% dextrose in 0.45% NaCl) to produce calcium diuresis. A calcium-wasting diuretic such as furosemide can be used with close monitoring of electrolytes. In cases of immobilization-induced hypercalcemia, bisphosphonate therapy has been shown to be effective. In the neonate or infant, low calcium formulas such as Calcilo XD may be substituted for more standard formulas to limit oral calcium intake.

43.10 Diabetes Insipidus and SIADH

43.10.1 Diabetes Insipidus

Central diabetes insipidus (CDI) may be caused by damage to the pituitary gland or hypothalamus (e.g., from surgery, trauma, infection, or tumors), systemic granulomatous conditions such as Langerhans cell histiocytosis (LCH),

Table 43.16 Clinical presentation for diabetes insipidus

Polyuria (>4 ml/kg/h)	Weight loss
Polydipsia	Poor growth
Poor sleep	Diarrhea
Fever	Vomiting
Irritable/inconsolable	

autoimmune disease, from a structural congenital anomaly (e.g., holoprosencephaly, absence of the corpus callosum, septo-optic dysplasia) or less commonly, from an inherited gene defect (*AVP-NPII, WFS1*). Congenital forms of nephrogenic diabetes insipidus (NDI) include X-linked NDI (90% of cases), which is caused by a mutation in the arginine vasopressin (AVP) receptor 2 *(AVPR2*) and the autosomal dominant and recessive forms of NDI (10% of cases), which occur when there is a mutation in the aquaporin 2 (AQP2) water channel. Nephrogenic diabetes insipidus may also be seen with chronic kidney disease, an electrolyte disturbance (e.g., hypercalcemia, hypokalemia), or NDI may be medication induced (e.g., lithium, antivirals, amphotericin B, rifampin).

The diagnosis of diabetes insipidus is confirmed in the presence of a high serum sodium concentration (>145 mEq/L), high serum osmolality (>300 mOsm/L), and low urine osmolality (<300 mOsm/L). Patients with diabetes insipidus usually present with classic symptoms (Table 43.16). A water deprivation test may be performed under close medical supervision to confirm the diagnosis and can help differentiate between CDI and NDI by directly measuring endogenous arginine vasopressin (AVP) at the conclusion of the test and by monitoring the clinical and biochemical response to exogenously administered DDAVP (desmopressin acetate). An elevated endogenous arginine vasopressin (AVP) concentration greater than 20 pg/mL at the conclusion of the test is highly likely to be NDI. The standard water deprivation test has had its challenges. It is often a long test to administer (may exceed 20 h), and it has been difficult to measure arginine vasopressin using the current assay. A study in 2018 showed that direct measurement of hypertonic-saline stimulated plasma copeptin had a greater diagnostic accuracy than the standard water deprivation test in distinguishing patients with partial DI from patients with primary polydipsia (95.2% vs. 73.3%, respectively). Copeptin is a glycopeptide derived from the same precursor as AVP and is secreted in an equimolar amount as AVP. A bolus of 250 mL of 3% saline was administered, followed by a continuous infusion of hypertonic saline at a rate of 0.15 mL per kg per minute with monitoring of plasma osmolality, sodium, urea and glucose levels every 30 minutes until the sodium reached 150 mmol per liter. A final blood sample for plasma copeptin was then obtained. A plasma copeptin level of 4.9 pmol or less was indicative of DI (complete or partial) while a level greater than 4.9 pmol was indicative of primary polydipsia.

Treatment of diabetes insipidus depends on whether the DI is central or nephrogenic. CDI is treated with DDAVP which can be administered IV in acute situations or by the intranasal or enteral route in subacute conditions (Table 43.17). The optimal dose depends on a patient's response and requires careful monitoring of fluid intake and urine output to prevent hyponatremia and water intoxication. Congenital NDI is best treated with dietary manage-

Table 43.17 Pediatric DDAVP dosing for diabetes insipidus

	[a]Oral (0.1 mg, 0.2 mg tabs)	Intranasal (0.01%)	SQ/IV (4 mcg/ml)
<4 years	0.1–0.8 mg/day divided BID	Start with 2.5 mcg q day to BID up to 30 mcg q day	0.1–1 mcg q day or divided BID (suggested but not defined)
4–12 years	0.1–1.2 mg/day divided BID-TID	Start with 2.5 mcg QD-BID up to 30 mcg QD	0.1–1 mcg QD or divided BID (suggested but not defined)
>12 years	0.1–1.2 mg/day divided BID-TID	Start with 5 mcg QD-BID up to 40 mcg QD	1–2 mcg BID

[a]Starting oral dose is 0.05 mg q day

A water deprivation test may be performed under closed medical supervision to confirm the diagnosis and can help differentiate between CDI and NDI by directly measuring endogenous AVP at the conclusion of the test and by monitoring the clinical and biochemical responses to exogenously administered DDAVP. A recent study showed that hypertonic saline infusion with measurement of copeptin at the conclusion of the test may be superior in discriminating between CDI and NDI and was less time consuming than the classic water deprivation test.

The diagnosis of diabetes insipidus is confirmed in the presence of a high serum sodium concentration, high serum osmolality, and low urine osmolality.

ment (low sodium, low protein, high calorie) with diuretics, such as hydrochlorothiazide and amiloride, and with nonsteroidal antiinflammatory drugs such as ibuprofen, indomethacin, and naproxen. Acquired NDI is best managed by determining and treating the underlying cause if possible.

43.10.2 Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

SIADH occurs when there is excessive secretion of antidiuretic hormone, which results in urinary water retention and hyponatremia. SIADH may be caused by meningitis, encephalitis, brain tumors, lung disease, medications, head trauma, or in the postoperative period (e.g., following hypothalamic pituitary surgery). Increased ADH may also be an appropriate response in some of these conditions if there is inadequate intravascular volume, such as due to sepsis or when there is reduced atrial filling, such as with positive pressure ventilation and lung disease characterized by hyperinflated lungs. Distinguishing between appropriate and inappropriate ADH secretion has therapeutic implications; for example, rather than fluid restriction, a patient on positive pressure ventilation may need increased fluid, at least initially, to preserve venous return and thus cardiac output.

Treatment involves managing the underlying pathology. Restriction of fluids to generate a negative fluid balance is appropriate if SIADH is suspected. Sometimes 3% normal saline (0.5–1 ml/kg/h), loop diuretics such as furosemide, urea and/or medications known to cause NDI, such as demeclocycline, and lithium carbonate may be needed. Although there is limited data in children, the selective vasopressin receptor antagonist, tolvaptan, when administered orally, was found to significantly increase serum sodium in 448 patients, in whom 190 had SIADH.

43.10.3 Cerebral Salt Wasting

Although the exact pathophysiology is unclear, cerebral salt wasting syndrome (CSWS) may complicate the postoperative care of pediatric brain tumor patients. In a cohort of 282 children, CSWS occurred more commonly than SIADH (5% vs. 3% of cases), and was associated most commonly with chiasmatic/hypothalamic tumors, although 60% of cases were associated with tumors in other brain locations. CSWS is more common in younger children and 40% of cases were associated with a postoperative stroke, which occurred in only 4.6% of eunatremic patients.

The onset was a median of 3 days after surgery and often recognized by the onset of seizures in association with severe hyponatremia. The diagnosis of CSWS was based on hyponatremia (Na < 135 mEq/L), elevated urine sodium (>120 mEq/L), and urine osmolality >300 mosm/kg. Patients often had markedly increased urine sodium excretion (mean urine sodium concentration of 235 mEq/L, range of 100–413 mEq/L), which explains the need to use an infusion of 3% saline to correct the sodium concentration and keep up with ongoing sodium loss. Fortunately, in most children, CSWS resolved in several days.

In addition to brain tumor patients, CSWS has been associated with other types of brain injuries such as head trauma and strokes. It is important to recognize the syndrome since hyponatremia due to CSWS is often assumed to be a sign of SIADH, but fluid restriction will lead to significant dehydration if not recognized and managed with the opposite therapy of increased fluid and sodium intake.

43.11 Endocrine Complications of Pediatric Brain Tumors

Endocrine dysfunction is a common occurrence in children with tumors of the central nervous system (CNS). Astrocytomas, medulloblastomas, ependymomas, and craniopharyngiomas represent the most common primary CNS tumors in children. Those who undergo surgery or radiation for solid tumors or leukemias often have hypothalamic and/or pituitary deficiencies that if left untreated can have devastating consequences. A complete hormonal evaluation is warranted both pre- and postoperatively in patients with CNS tumors to assess hormone secretion and to rule out pituitary insufficiency. These endocrine studies should include morning cortisol and ACTH, TSH and free T4, IGF-1, FSH, LH, and testosterone levels (in males) or estradiol levels (in females).

A complete hormonal evaluation is warranted pre- and postoperatively in patients with CNS tumors to assess hormone secretion and to rule out pituitary insufficiency.

In preparing a patient for pituitary surgery, a stress dose of hydrocortisone is administered (50–100 mg/m^2/day) which is usually continued postoperatively until formal testing of the hypothalamic-pituitary-adrenal axis can be assessed. Partial or complete hypopituitarism and/or central diabetes insipidus (CDI) may occur after surgery or radiation of CNS tumors.

Disturbances of osmoregulation are commonly encountered in patients following pituitary-hypothalamic surgery. A variety of factors contribute to the polyuria often seen postoperatively. Large amounts of fluid are often administered perioperatively. High-dose corticosteroids, which are known to increase free water excretion, are often given to patients pre- or intraoperatively to prevent cerebral edema. A "triple phase" of polyuria, oliguria with hyponatremia, and polyuria may be observed postoperatively. The initial phase of transient diabetes insipidus may be seen in the first 12–24 h with surgical destruction of vasopressin neurons. A second phase of SIADH often follows as vasopressin is

released from dying neurons. Stress and pain are also strong stimuli of AVP secretion. This phase may last up to 10 days. The third phase of permanent diabetes insipidus occurs if more than 90% of vasopressin cells have been destroyed. As previously noted, CSWS may complicate surgery for brain tumors.

It is important to know that in patients with coexistent cortisol deficiency, free water excretion is impaired such that symptoms of diabetes insipidus are masked. In these cases, upon initiation of glucocorticoids, polyuria ensues leading to the diagnosis of diabetes insipidus. Care should be taken to prevent complications that may arise in the postoperative period in patients who have undergone hypothalamic-pituitary surgery. Fluid intake and urine output should be monitored closely. Given the postoperative pattern of polyuria and oliguria/hyponatremia, desmopressin should be used judiciously. Other hormones for which the patient may be deficient should also be replaced when indicated.

A "triple phase" of polyuria, oliguria with hyponatremia, and then polyuria may be observed in patients with CNS tumors following pituitary-hypothalamic surgery.

Patients who have undergone CNS/pituitary surgery require lifelong monitoring and management as indicated by clinical and biochemical findings. Those who undergo postoperative radiation are at risk for developing new pituitary hormone deficiencies. Thus, it is imperative that patients receive regular evaluations to assess their need for additional treatment and hormone replacement.

43.12 Tight Glucose Control

Hyperglycemia and glucose intolerance have been observed in critically ill adults and children for many decades. Early studies in the 1970s, focusing on the metabolic derangements in sepsis and critical illness, demonstrated a relatively insulin-resistant hyperglycemia with elevated levels of insulin and counter-regulatory hormones (epinephrine, cortisol, and growth hormone). Hyperglycemia has long been known to be a marker for the metabolic derangements associated with critical illness as well as an independent predictor of poor outcome. For many years some degree of hyperglycemia was an accepted metabolic response to critical illness and insulin was used only sparingly to reduce blood glucose levels below the renal threshold to prevent unwanted osmotic diuresis.

Intensive insulin therapy has been associated with improvement in the serum levels of inflammatory markers and in some studies a reduction in mortality in the critically ill.

There are a number of postulated mechanisms by which tight glucose control could affect outcome. These include reducing cellular glucose toxicity, glucose toxicity to the mitochondria, effects on the innate immune system, inflammatory modulation, and improving neuromuscular function. Insulin may be able to counteract some of the catabolism associated with critical illness in addition to having possible antiinflammatory and antiapoptotic properties.

In 2009, Vlasselaers and others evaluated tight glucose control in a pediatric critical care population; ~75% of the children were postop cardiac surgery. They reported that when compared to the conventional treatment group, the children in the intensive insulin treatment group had a shorter duration of PICU stay, lower CRP levels at day 5, and a trend toward lower mortality. The largest study of tight glucose control, the NICE-SUGAR Study, enrolled more than 6000 adult patients in intensive care units in Australia, New Zealand, and Canada. Reported in 2009, the study demonstrated that severe hypoglycemia was much more likely in the intensive glucose control group compared with

conventional insulin therapy. There was also no significant difference between the two treat treatment groups in the median number of days in the ICU, hospital days, median number of days on mechanical ventilation, or rate of renal replacement therapy. Mortality was slightly greater in the intensive control group.

A 35-center trial involving 713 critically ill children published in the *New England Journal of Medicine* in 2017 was stopped early for futility and concern about the potential for increased harm from severe hypoglycemia in the intensive treatment group. The authors concluded that critically ill children with hyperglycemia did not benefit from tighter glycemic control (defined as blood glucose level 80–110 mg/dL) in comparison to those with higher blood glucose levels of 150–180 mg/dL. Patients with tighter glycemic control also had higher rates of healthcare-associated infections as well as higher rates of severe hypoglycemia (blood glucose < 40 mg/dL) than those with slightly higher blood glucose levels. Since a posthoc analysis of the larger NICE-SUGAR study noted a significant association between higher mortality and the occurrence of moderate or severe hypoglycemia, it suggests, but does not prove, that there is increased morbidity/mortality in children managed with tight glucose control.

The largest study of tight glucose control, the NICE-SUGAR Study, enrolled more than 6000 adult patients and showed no improvement in mortality with intensive insulin therapy. A subsequent multicenter pediatric trial also failed to show any benefit from tight glucose control.

Studies of intensive insulin therapy in the ICU setting have demonstrated that the development of hypoglycemia appears to be detrimental and associated with increased mortality.

In summary, conflicting studies have left some uncertainty as to whether tight glucose control is indeed beneficial for the critically ill and whether this benefit extends to all or just some subsets of the critically ill. What does seem to be clear is that the development of hypoglycemia appears to be detrimental and increases mortality. What remains to be determined is whether there is a threshold for glucose control that would both confer benefit yet minimize the risk of harmful hypoglycemia. In addition, the applicability of adult data to pediatrics may not be relevant since critically ill children may behave differently from critically ill adults, particularly with regard to the risk for late mortality.

43.13 Summary

Hormones play a crucial role in the maintenance of homeostasis. If an individual is unable to adapt when this equilibrium is challenged with either intrinsic or extrinsic stressors, metabolic decompensation ensues. Proper management of endocrinologic emergencies involves early recognition of signs and symptoms that may be nonspecific. Such conditions, if left untreated, can result in catastrophic consequences. Obtaining baseline blood and urine samples at the time of presentation (including archival samples for specialized testing if indicated) provides important diagnostic information that can aid in the long-term management of these patients and in the prevention of metabolic crises.

Review Questions

1. A 2-year-old male presents with lethargy and a brief, self-limiting, generalized, tonic clonic seizure. His parents report that he has had an intercurrent viral illness for the past few days characterized by fever, anorexia, and upper respiratory symptoms. Point of care testing reveals a blood glucose level of 38 mg/dL. Urinalysis is strongly positive for ketones but is otherwise unremarkable. $D_{25}W$ is administered as a 2 mL/kg bolus. Insulin levels drawn at the time of hypoglycemia are subsequently found to be less than 2 μIU/mL. Which of the following is the most likely diagnosis?
   A. Disorder of fatty acid oxidation
   B. Galactosemia
   C. Glycogen storage disease
   D. Hyperinsulinism
   E. Ketotic hypoglycemia

2. Which of the following statements is true concerning childhood hypoglycemia?
   A. Approximately one-third of children under the age of 5 years with acute gastroenteritis are found to be hypoglycemic at presentation.
   B. Children with glycogen storage diseases are profoundly symptomatic with hypoglycemia as a result of their impaired ability to utilize lactate and ketones.
   C. Galactosemia is the most common cause of hypoglycemia in the neonatal age group.
   D. Hyperinsulinism is the most common cause of hypoglycemia in the preschool age group.
   E. Ketotic hypoglycemia is characterized by hypoglycemia following fasting with ketonemia and elevated serum insulin levels.

3. Which of the following interventions is associated with an increased risk of cerebral edema in children with diabetic ketoacidosis?
   A. Failure to administer an insulin bolus prior to initiating an insulin infusion
   B. Inadequate rate of fluid administration
   C. The administration of mannitol
   D. The use of 0.9% normal saline for intravenous fluid
   E. Treatment with intravenous sodium bicarbonate

4. A 16-year-old obese female presents with a 3–4 month history of polyuria, polydipsia, and a 20 pound weight loss. Her initial plasma glucose is 755 mg/dL, and her urinalysis shows glycosuria and moderate ketonuria. Which of the following complications is this child at highest risk for developing?
   A. Hypoglycemia
   B. Hypochloremic acidosis
   C. Hypocalcemia
   D. Severe hypophosphatemia
   E. Hyperkalemia

5. Which of the following statements is true regarding adrenal insufficiency in critically ill children?
   A. A baseline serum cortisol level <25 μg/dL during a period of stress is consistent with adrenal insufficiency.
   B. A single dose of etomidate may increase the risk of adrenal insufficiency during pediatric critical illness.
   C. Failure of the serum cortisol level to rise more than 50 μg/dL 30 min after the administration of intravenous cosyntropin is consistent with adrenal insufficiency.
   D. The daily glucocorticoid maintenance dose for patients with known adrenal insufficiency is 25–50 mg/m^2/day of intravenous hydrocortisone.
   E. There is strong evidence for a beneficial effect of glucocorticoid treatment on mortality in critically ill children.

6. Which of the following laboratory findings distinguishes euthyroid sick syndrome from primary hypothyroidism?
   A. Euthyroid sick syndrome is characterized by a normal TSH, low T3, and high free T3 while primary hypothyroidism is characterized by an elevated TSH, low T4, and low free T4.
   B. Euthyroid sick syndrome is characterized by a normal TSH, low T3, and normal to increased reverse T3 while primary hypothyroidism is characterized by an elevated TSH, low T4, and low free T4.

C. Euthyroid sick syndrome is characterized by a normal TSH, low T4, and low free T4 while primary hypothyroidism is characterized by an elevated TSH, low T4, and low free T4.
D. Euthyroid sick syndrome is characterized by an elevated TSH, low T3, and low free T3 while primary hypothyroidism is characterized by an elevated TSH, low T4, and low free T4.
E. Euthyroid sick syndrome is characterized by an elevated TSH, low T4, and normal to increased reverse T3 while primary hypothyroidism is characterized by an elevated TSH, low T4, and low free T4.

7. A 5-year-old female is suspected to have hypothyroidism based on an elevated TSH level and a low free T4. She is treated with thyroid hormone replacement and, shortly thereafter, develops fever, vomiting, hyponatremia, hypoglycemia, and hypotension. Which of the following statements is the MOST likely explanation for this clinical scenario?
   A. Her thyroid function tests are more indicative of euthyroid sick syndrome, and the unnecessary thyroid hormone replacement likely precipitated the clinical collapse.
   B. She has a co-existing adrenal insufficiency, which has been exacerbated by the thyroid hormone-induced increased metabolic clearance of cortisol.
   C. She has received an inadequate dose of thyroid hormone and is manifesting symptoms of progressive hypothyroidism.
   D. She likely received an excessive dose of thyroid hormone precipitating the clinical collapse.
   E. She should be started on an infusion of dopamine because dopamine stimulates thyroid function and increases thyroid hormone levels.

8. Which of the following statements is true regarding diabetic ketoacidosis?
   A. A fall or diminished rise in serum sodium concentration during rehydration is linked to an increased risk of significant cerebral edema.
   B. Cerebral edema is most likely to occur in an adolescent who has incurred previous episodes of diabetic ketoacidosis.
   C. Low blood urea nitrogen levels have been associated with an increased risk of cerebral edema among patients with diabetic ketoacidosis.
   D. Sodium bicarbonate is effective in ameliorating intracellular cerebral acidosis.
   E. The development of hypernatremia during resolution of ketoacidosis is linked to an increased risk of significant cerebral edema.

9. A 6-month-old male is admitted to the pediatric intensive care unit with a diagnosis of hypovolemic shock secondary to acute gastroenteritis with profuse diarrhea. Point of care blood testing reveals an ionized calcium concentration of 0.80 mmol/L (normal range 1.15–1.27 mmol/L). Further testing reveals a persistently low ionized calcium concentration with a normal vitamin D level and a low parathyroid hormone level. In addition to calcium supplementation, administration of which of the following is MOST likely to help correct the hypocalcemia?
   A. Dextrose containing solution
   B. Magnesium sulfate
   C. Potassium chloride
   D. Potassium phosphate
   E. Sodium bicarbonate

10. A 12-year-old female undergoes a transsphenoidal approach to remove a craniopharyngioma. On postoperative day #7, her urine output decreases, serum osmolality and sodium are decreased, and urine specific gravity is increased. What is the most likely diagnosis?
    A. Diabetes insipidus
    B. Mineralocorticoid deficiency
    C. Adrenal insufficiency
    D. Diabetes mellitus
    E. Syndrome of inappropriate antidiuretic hormone secretion

Answers

1. E
2. A
3. E
4. D
5. B
6. B
7. B
8. A
9. B
10. E

Suggested Readings

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Metabolic Crises

Kevin A. Strauss

Contents

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» What is food to one, is to others bitter poison. (Titus Lucretius Carus (99–55 BC))

Learning Objectives

- Review the biochemistry and physiology of metabolic homeostasis
- Understand metabolic aspects of the biological stress response and the pathophysiology of inborn errors of metabolism (IEMs)
- Recognize common clinical presentations of metabolic disorders in the intensive care setting
- Understand how to use laboratory studies to diagnose and manage patients with IEMs
- Understand general principles of treatment for IEMs, focusing on suppression of catabolic pathways and enhancing the clearance of toxic metabolites
- Recognize and treat organ-specific toxicities that accompany metabolic crises, most notably cerebral edema, cardiomyopathy, hepatopathy, rhabdomyolysis, pancreatitis, and nephropathy

44.1 Introduction

Intermediary (or intermediate) metabolism provides cells with vital energy and building blocks via an integrated set of transport processes and chemical reactions.

Anabolism encompasses all energy-consuming syntheses of complex molecules and *catabolism* refers to their energy-liberating degradation.

Inborn errors of metabolism (IEMs) disrupt the flow of energy and substrates between cytosolic macromolecules (glycogen, protein, and fat) and their catabolic end-products.

Metabolism, derived from the Greek word for "change," represents the full set of chemical reactions that sustain life. The term "intermediary" (or "intermediate") metabolism is reserved for a subset of transport processes and chemical interconversions that provide energy for vital activities and assimilate nutrients into tissues. Intermediary metabolism is further divided into two broad categories: *anabolism*, energy-consuming syntheses of complex molecules from simpler ones, and *catabolism*, energy-generating reactions that degrade molecules into their constituent parts.

Intermediary metabolic reactions are grouped into pathways, each comprised of enzymes arranged in a sequence or cycle. Viewed from the catabolic perspective, these pathways originate with glycogen, protein, and triacylglycerol (macromolecular aggregates of sugars, amino acids, and fatty acids, respectively), intersect at key substrates (e.g., glucose-6-phosphate, pyruvate, and acetyl-coenzyme A [CoA]), converge upon the tricarboxylic acid (TCA) cycle, and feed reducing equivalents (NADH, $FADH_2$) into the mitochondrial electron transport chain (ETC) to produce energy in the form of adenosine triphosphate (ATP)(◘ Fig. 44.1). There is strong evolutionary conservation of this scheme across a broad range of species, underscoring its indispensable role in living organisms.

In humans, metabolic systems are embedded within a complex homeostatic framework that allows the flow of energy and materials to adapt to environmental changes and biological stress. Specifically, metabolic adaptation *in vivo* depends on exchange of substrates between organs, each of which has a distinctive pattern of enzyme activity that shifts under the influence of autonomic and endocrine control. Interorgan metabolic flux is further mediated by binding and transport proteins, deficiencies of which can cause disease. Rate-limiting metabolic enzymes often depend on vitamin cofactors and are commonly subject to regulation by feedback inhibition, phosphorylation-dephosphorylation, and transcriptional control (◘ Fig. 44.2).

"Inborn errors of metabolism" (IEMs), or simply "metabolic disorders," encompass the large and diverse spectrum of heritable monogenic conditions that interfere with one or more intermediary chemical reactions and, more

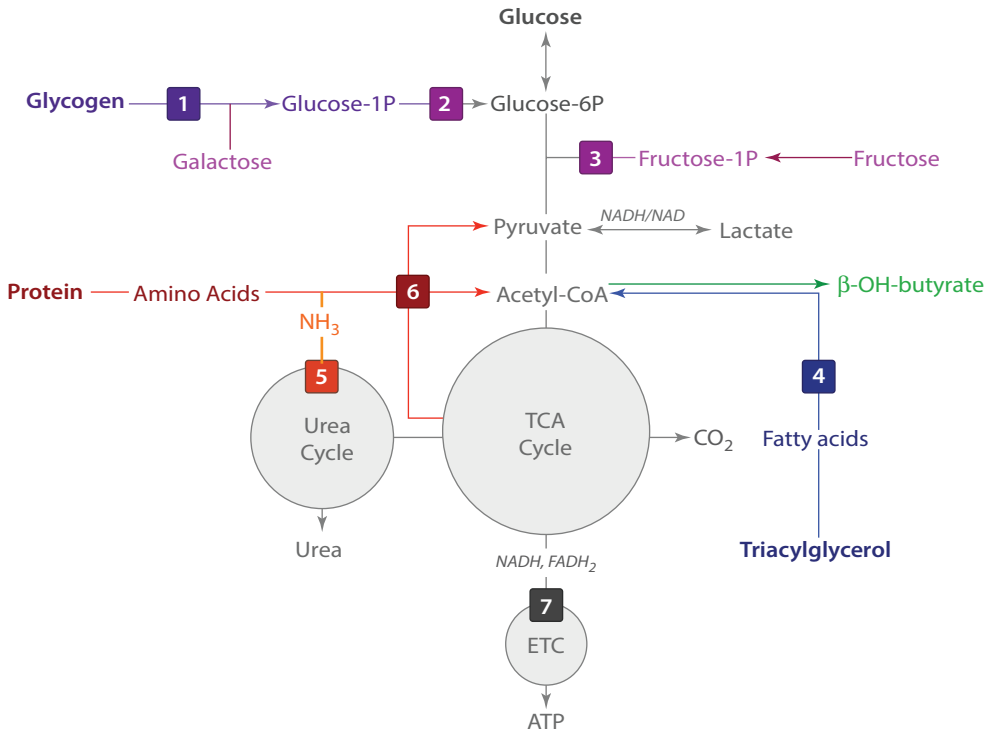

Fig. 44.1 Intermediary metabolism. Intermediary metabolic reactions begin with macromolecules (glycogen, triacylglycerols, and protein) and converge on the tricarboxylic acid (TCA) cycle and electron transport chain (ETC) to produce adenosine triphosphate (ATP). Pathways most relevant to the diagnosis and treatment of metabolic crises include glycogenolysis (1), galactose metabolism (2), fructose metabolism (3), fatty acid oxidation (4), ureagenesis (5), organic acid metabolism (6), and oxidative phosphorylation (7)

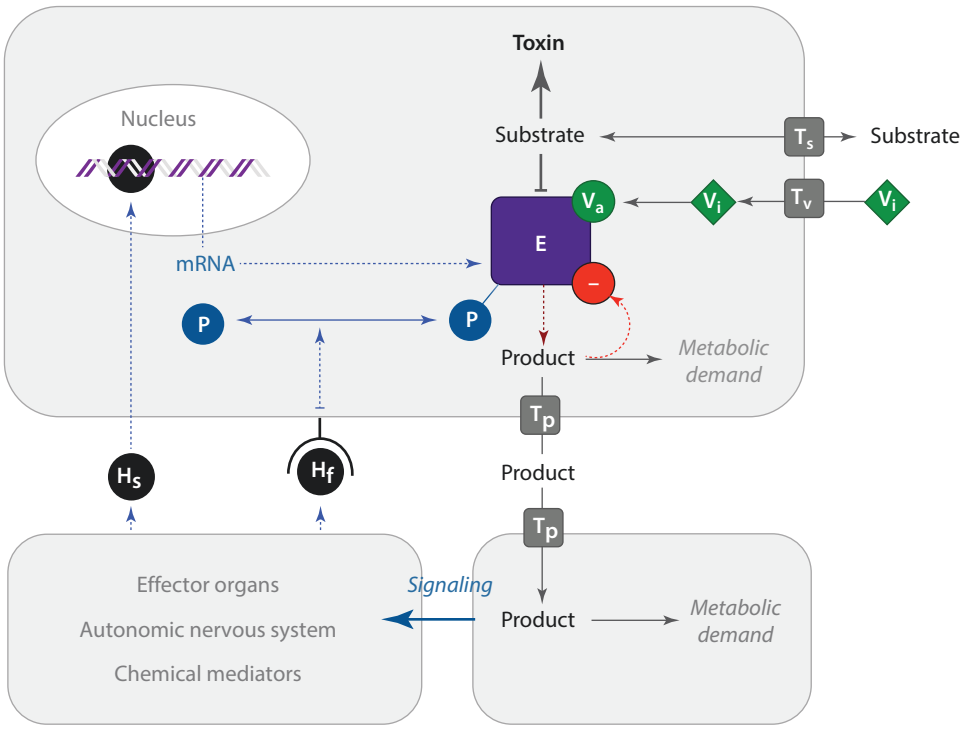

Fig. 44.2 Enzyme regulation and mechanisms of disease. Deficiency of a metabolic enzyme (E) results in accumulation of its substrate and a paucity of its product. Many rate-limiting enzymes are subject to regulation by feedback inhibition, phosphorylation-dephosphorylation (P), and transcriptional control and commonly depend on active vitamin cofactors (V_a) derived from inactive dietary forms (V_i). Enzyme activity changes under the influence of fast (H_f) and slow (H_s) modulatory signals, such as hormones and their related second messengers. Metabolic substrates and cofactors traverse biological membranes via specific transports (T), defects of which can cause disease

broadly, metabolic homeostasis. Both autosomal and mitochondrial DNAs encode enzymes of intermediary metabolism. Most IEMs segregate in an autosomal recessive fashion, but some follow dominant, X-linked, or mitochondrial patterns of inheritance.

A comprehensive review of strategies used to diagnose, categorize, and treat IEMs is beyond the scope of this chapter. Here, the emphasis is on practical aspects of metabolic physiology that allow for timely recognition and supportive treatment of metabolic crises in the pediatric intensive care unit (PICU). Specifically, this chapter focuses on two clinical paradigms – intoxicating encephalopathy and impaired fasting adaptation – most likely to cause acute, critical illness. Four open access projects online (see ▶ Sect. 44.9) are invaluable resources for the busy clinician seeking more detailed information about a particular metabolic condition:

- Online Mendelian Inheritance in Man (▶ https://www.omim.org/)
- GeneReviews (▶ https://www.ncbi.nlm.nih.gov/books/NBK1116/)
- National Organization for Rare Disorders (▶ https://rarediseases.org)
- Genetics Home Reference (▶ https://ghr.nlm.nih.gov)

44.2 Pathophysiology

Metabolic disorders can cause disease by at least three mechanisms: deficiency of critical energy substrates (e.g., glucose, β-hydroxybutyrate), accumulation of intoxicating metabolites in the circulation (e.g., ammonia, leucine), or production of endogenous cytotoxins (e.g., galactose-1-phosphate, unmetabolized acyl-CoA thioesters).

Deficiency of a metabolic enzyme, cofactor, or transport system can cause disease by at least three mechanisms (◘ Fig. 44.2): (1) insufficiency of a vital metabolic fuel (e.g., glucose, β-hydroxybutyrate); (2) accumulation of a proximal substrate (e.g., ammonia, leucine); or (3) production of a cellular intermediate (e.g., acyl-CoA thioesters in mitochondria, glutamine in astrocytes, galactose-1-phosphate in hepatocytes) that exerts tissue-specific toxicity. Accordingly, the foundation of therapy for acute metabolic crises is exogenous replacement of energy (e.g., glucose) coupled to rapid reduction of cytotoxins in the circulation and vital organs. Both goals are achieved through coordinated efforts to oppose the counterregulatory response, shift fuel metabolism toward an anabolic state, and implement active clearance strategies.

44.2.1 Biological Stress Response

Autonomic and endocrine actions of the biological stress response degrade tissue glycogen, fat, and protein to supply the brain, skeletal muscle, and other vital organs with glucose and β-hydroxybutyrate.

Common iatrogenic stresses in the ICU include intravenous glucocorticoids, vasoactive catecholamines, and undertreated pain and psychological distress, all of which drive tissue catabolism.

Pathways of intermediary metabolism most pertinent to critical care medicine mediate glucose homeostasis, fatty acid oxidation, oxidative phosphorylation, amino acid degradation, and the processing of nitrogenous waste (◘ Fig. 44.1). Restricted flow through any one of these pathways can manifest with the type of sudden, catastrophic decompensation that presents to the pediatric intensivist. Metabolic crises typically occur in the context of a "triggering" challenge and thus reflect a failure of stress adaptation. The biological stress response consists of interrelated autonomic, endocrine, inflammatory, and behavioral changes that are initiated by the central nervous system and have evolved to ensure survival of the organism. Interorgan metabolic flows serve a core strategy: to supply the brain and other vital organs with fuel (glucose and β-hydroxybutyrate) by accessing energy stored in the form of glycogen, triacylglycerol, and nonessential muscle protein (◘ Fig. 44.3).

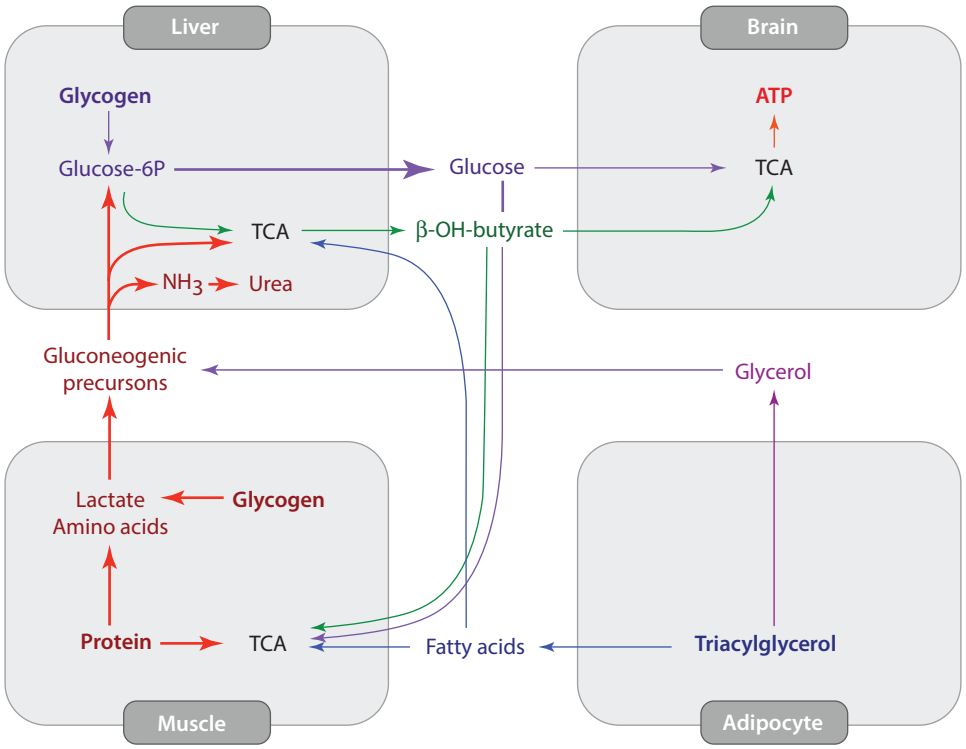

Fig. 44.3 Interorgan substrate flow in response to biological stress. The metabolic adaptation to stress is comprised of integrated flows between organs that supply the brain and other vital tissues with fuel (glucose and β-hydroxybutyrate) by accessing energy stored in the form of glycogen, triacylglycerol, and nonessential muscle protein. *Abbreviations*: *ATP* adenosine triphosphate, *TCA* tricarboxylic acid cycle

Specific elements of stress adaptation are especially pertinent to the management of patients. Normally, the brain receives afferent signals about various internal threats (e.g., microbial invasion, tissue injury, hypoglycemia, dehydration) which in turn trigger activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis. Sympathetic outflow stimulates glucagon release and inhibits insulin release from the endocrine pancreas. Sympathetic actions combined with the cellular effects of glucagon, epinephrine, growth hormone, and cortisol (collectively termed counterregulatory hormones) underlie the catabolism of carbohydrate, fat, and protein across a network of organs (Fig. 44.3). Cortisol plays a permissive role via transcriptional upregulation and downregulation of rate-limiting metabolic enzymes in liver, adipose tissue, and muscle.

Biological stress can expose defects in diverse chemical pathways and is, therefore, central to the generation and perpetuation of metabolic crises (Fig. 44.1). This fact has special weight in the PICU, where infants and children face serious physiologic threats such as hypoglycemia, trauma, respiratory failure, sepsis, and shock. Iatrogenic stress is also common in the ICU and can exacerbate metabolic illness. Glucocorticoids and vasoactive catecholaminergic agents, although sometimes lifesaving, drive tissue catabolism, and undertreated pain and/or anxiety also activates the counterregulatory system.

44.2.2 Glucose Homeostasis and Metabolic Adaptation to Fasting

The young brain is especially vulnerable to severe (<20 mg/dL), recurrent (≥3 episodes), or prolonged hypoglycemia.

Normal adaptation to fasting protects the brain against hypoglycemia and is divided into (I) post-prandial, (II) glycogenolytic, (III) gluconeogenic, and (IV) ketogenic phases. The timing of these adaptations can be compressed in individuals who are young, malnourished, or critically ill.

Endogenous glucose production rate (EGPR, in mg/kg•min) represents the combined actions of glycogenolysis and gluconeogenesis, meets 40–60% of total energy demand, and decreases with age.

Hyperinsulinemic children manifest hypoketotic hypoglycemia in close proximity to feeding and require supraphysiologic glucose infusions (e.g., 2-times EGPR) to maintain euglycemia; defective fatty acid oxidation is revealed later in the course of fasting and is easily stabilized with glucose infusions ≤EGPR.

Neural tissue requires a continuous supply of glucose over the arc of life. The brain consumes 30–35% of resting energy expenditure (REE) in newborns and its proportional demand peaks at ~65% by age 5 years (Fig. 44.4). The brain is especially vulnerable to hypoglycemia during this early phase of growth and synaptogenesis. As the ratio of brain to body weight decreases thereafter, so too does cerebral energy demand as a proportion of the REE.

There is no fixed definition of hypoglycemia. Recommended thresholds are based on observed physiologic and behavioral changes in response to declining blood glucose concentrations (Table 44.1). Extrapolating from these data, glucose concentrations <47 mg/dL (2.6 mmol/L) are commonly defined as hypoglycemia whereas values <36 mg/dL (<2.0 mmol/L) are widely accepted as dangerous. From a neurophysiological perspective, these thresholds are not particularly age dependent, but neuroglycopenia has special implications in young patients. Blood glucose concentrations <36 mg/dL during infancy and early childhood are associated with long-term visuomotor and executive impairments, and blood glucose concentration <20 mg/dL in newborns can precipitate irreversible neuronal and white matter injury. Neurological risk increases when hypoglycemia is prolonged or recurrent (≥3 episodes).

An elaborate metabolic defense system has evolved to safeguard the brain against hypoglycemia during periods of insufficient intake or increased demand (Fig. 44.3). This stereotyped adaptation depends on normal activity of glycogenolytic, gluconeogenic, and fatty acid oxidation pathways and is heuristically divided into four phases (Fig. 44.5):

I. Exogenous glucose is oxidized for 2–3 hours following a meal.
II. As exogenous supply wanes, hepatic glycogenolysis releases glucose to the circulation.
III. Glycogen stores dwindle 4–16 hours into fasting as the predominant source shifts to gluconeogenesis, a process which makes glucose from glycerol, amino acids, and lactate (Cori cycle) using energy from fatty acid oxidation.
IV. During the final phase of adaptation, brisk ketogenesis provides alternative fuel (β-hydroxybutyrate) for the brain and vital organs, reducing the body's demand for glucose.

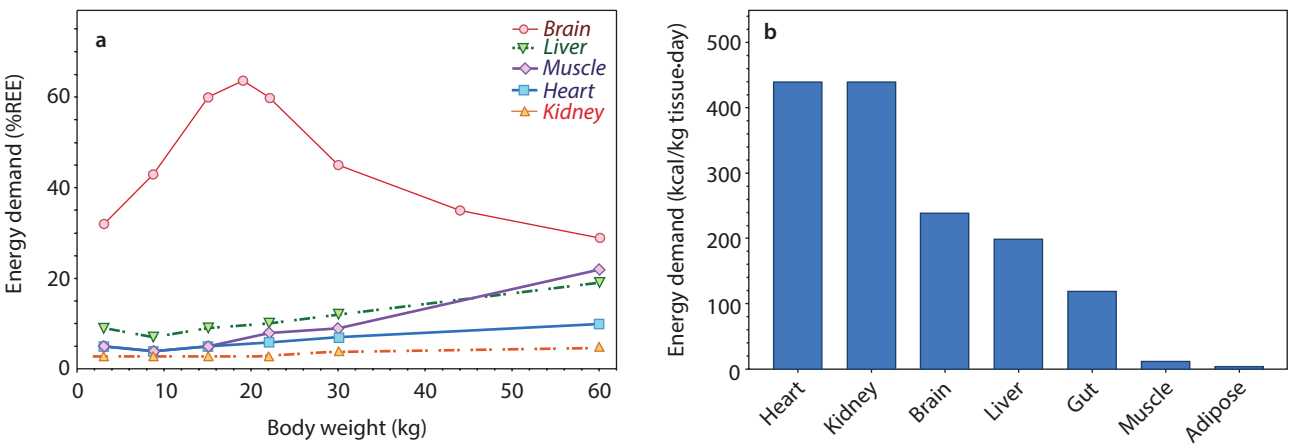

Fig. 44.4 Anatomical and maturational distribution of energy demand. (**a**) Interorgan distribution of resting energy expenditure (REE) shifts over the lifespan. The newborn brain (red circles) comprises 12–15% of body mass and accounts for 30–35% of energy expenditure. By late adolescence, muscle (purple diamonds) represents 30–40% of body mass and most of the body's energy expenditure is equally distributed among brain, skeletal muscle, and liver (green triangles). (**b**) At all ages, cardiac myocytes (blue squares) and kidney cells (orange triangles) have the highest energy demand per weight of tissue

Table 44.1 Physiological and behavioral changes associated with hypoglycemia

Blood glucose			
mgldL	*mmollL*	**Physiological changes**	**Behavioral changes**
55–60	3.0–3.3	CBF increased	Cognitive function preserved
		CMR_{glu} preserved	Consciousness preserved
		CMR_{ox} preserved	
36–46	2.0–2.6	CMR_{glu} decreased	Impaired cognition
		CMR_{ox} preserved	Slowed reaction time
		Increased AEP and VEP latencies	
<36	<2.0	CBF increased 50–60%	Cognitive slowing
		CMR_{glu} decreased	Slurred speech, ataxia
		CMR_{ox} preserved	Diaphoresis, pallor, tremor
		Depletion of intracerebral glucose	Stupor, obtundation
<18	<1.0	Depletion of cerebral glycogen	Seizures
		Electrographic seizures	Coma
		Isoelectric brain waves	

Abbreviations: AEP auditory evoked potentials, *CBF* cerebral blood flow, CMR_{glu} cerebral metabolic rate for glucose, CMR_{ox} cerebral metabolic rate for oxygen, *VEP* visual evoked potentials [Adapted from Plum and Posner (2007), *Suggested Readings*]

The timing of these metabolic adaptations can be compressed in individuals who are young, malnourished, or critically ill.

Glycogen comprises 5–8% of liver mass, which in children represents 2.7–4.2% of body weight. Thus a 15 kg child with a 400–600 gram liver stores 20–50 grams of glycogen, enough to supply the body with glucose for 4–9 hours. Consistent with this observation, approximately 40% of pediatric surgical patients managed with hypocaloric infusions (2.5% dextrose) develop ketosis, with or without overt hypoglycemia, 4–16 hours into fasting.

Endogenous glucose production rate (EGPR) during phases II–IV of fasting represents the combination of glycogenolysis and gluconeogenesis and normally maintains blood glucose well above the neuroglycopenic threshold (Fig. 44.6). Endogenous glucose production was first measured directly in 1977 using the nonradioactive tracer 6,6-dideuteroglucose. In 2014, this same method was used to generate a nonlinear regression equation that estimates EGPR (expressed in mg/kg•min) from infancy to adulthood:

$$\text{EGPR} = 6.50 \times 2.72^{-0.145 \times \text{age in years}} + 1.93$$

At all ages, EGPR matches or exceeds the brain's demand for glucose by meeting 40–60% of total energy demand.

A counterregulatory response is triggered by blood glucose concentrations between 50 and 70 mg/dL (2.8–3.9 mmol/L), which is 30–50% above the threshold for neuroglycopenia. This response is mediated by the sympathetic nervous system and several hormones (glucagon, epinephrine, and cortisol; Fig. 44.6) and can expose defects within the metabolic defense system. The timing of hypoglycemia signals the pathway involved: disorders of glycogenolysis commonly manifest during the early stage of fasting (phase II; 4–16 hours), whereas

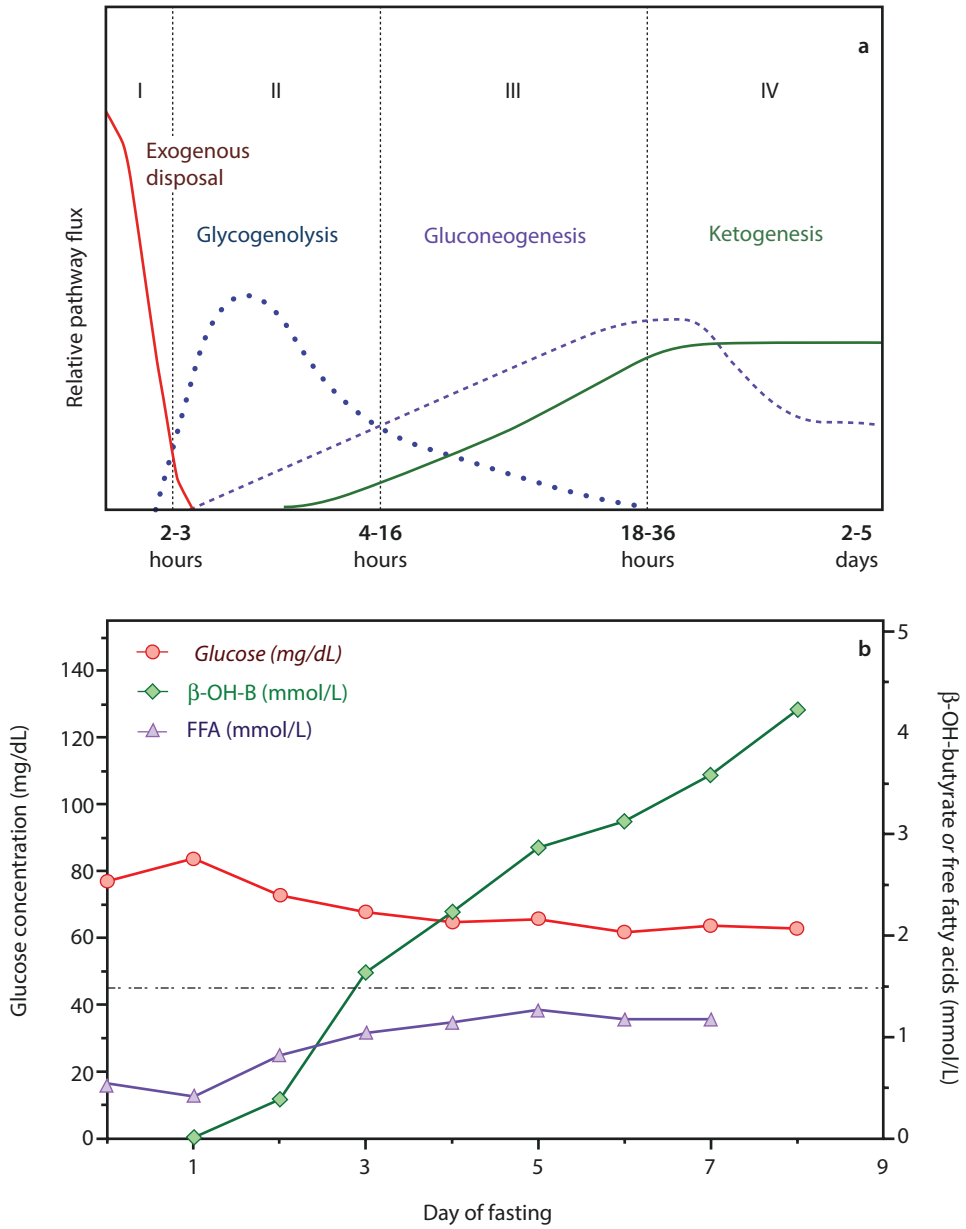

Fig. 44.5 Metabolic adaptation to fasting. (**a**) Exogenous glucose is oxidized within 2–3 hours of a meal (phase I). As this exogenous supply wanes, the liver begins to degrade glycogen (phase II). Glycogen stores dwindle 4–16 hours into fasting when the predominant source of circulating glucose becomes gluconeogenesis (phase III), which makes new glucose from the carbon skeletons of glycerol and amino acids using energy supplied by fatty acid oxidation. During the final stage of adaptation (phase IV), brisk ketogenesis reduces the body's overall demand for glucose. The timing of these phases can be compressed in individuals who are young, malnourished, or critically ill. (**b**) In healthy fasting adults, endogenous glucose production from glycogenolysis and gluconeogenesis maintains blood glucose (red circles) well above the neuroglycopenic threshold (~46 mg/dL; gray dashed line). Free fatty acids (purple triangle) and β-hydroxybutyrate (green diamonds) increase after 24 hours, underscoring the importance of fatty acid oxidation during prolonged fasting. (Adapted from Cahill (2006), *Suggested Readings*)

children with fatty acid oxidation disorders can fast longer but become hypoglycemic precipitously in the absence of ketogenesis. Under controlled conditions, infants with medium-chain acyl dehydrogenase deficiency (ACADM; OMIM 201450) develop hypoglycemia after 12–20 hours of fasting; affected children >1 year of age become hypoglycemic within 18–32 hours.

Hypoketotic hypoglycemia is particularly dangerous, depriving neural tissue of its two main fuels, and should always raise suspicion of a fatty acid oxidation disorder. Familial hyperinsulinemia (OMIM PS256450) is the only

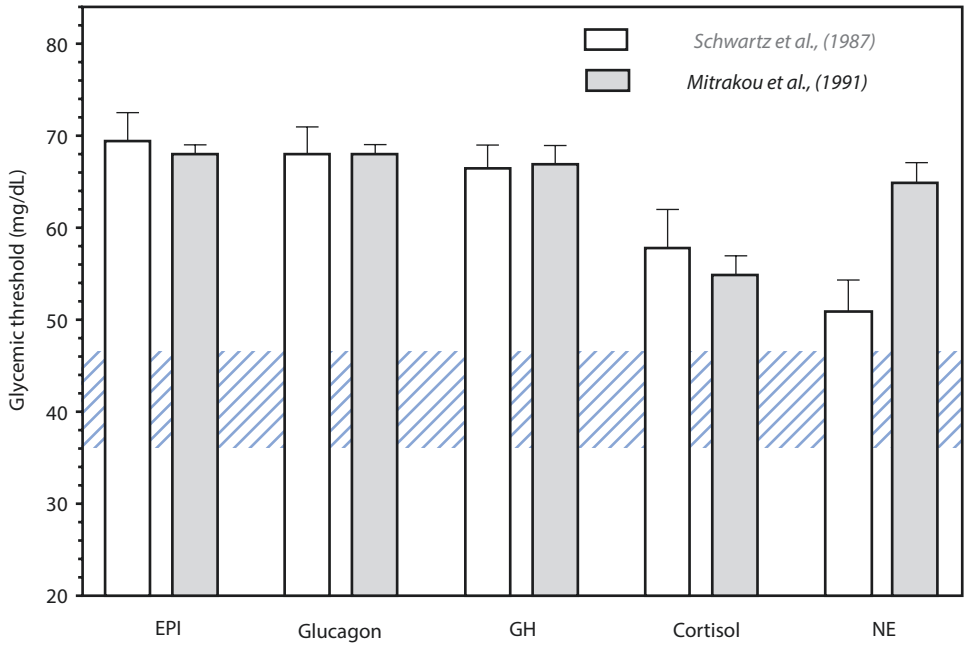

Fig. 44.6 Counterregulatory response to hypoglycemia. Sympathetic activation triggers release of, and acts in concert with, the counterregulatory hormones epinephrine (EPI), glucagon, growth hormone (GH), and cortisol to defend against hypoglycemia and drive metabolic adaptations to stress through both fast and slow modulatory mechanisms. The glycemic threshold, plotted on the y-axis, is the glucose concentration at which increased secretion of a hormone or neurotransmitter is first detected in arterialized plasma. The counterregulatory system is activated at blood glucose concentrations of 50–70 mg/dL (2.8–3.9 mmol/L), well above the threshold for neuroglycopenia (blue shaded area). Increased plasma norepinephrine (NE) represents activation of the sympathetic nervous system in response to hypoglycemia. (Data redrawn from Schwartz et al. (1987) and Mitrakou et al. (1991), *Suggested Readings*)

other Mendelian condition that produces this pattern but can be readily distinguished from disorders of fatty acid oxidation: (1) hyperinsulinemia causes hypoketotic hypoglycemia during post-prandial phase I, in close proximity to feeding, whereas disorders of fatty acid oxidation are revealed later in fasting (phases III–IV); and (2) hyperinsulinemic children require supraphysiologic infusions of dextrose (e.g., 2-times EGPR), whereas children with fatty acid oxidation disorders remain euglycemic on dextrose infusions ≤ EGPR.

44.2.3 Protein Turnover and Endogenous Intoxication

Like glucose homeostasis and counterregulation, the protein economy and its response to biological stress are fundamental to understanding and treating volatile IEMs. Fourteen percent of human body mass is protein, 75–79% of which is intracellular. For the purpose of understanding metabolic decompensation and reversal, intracellular protein (~10–12% of body mass) represents a labile metabolic pool subject to rapid accretion and degradation in response to various hormonal, autonomic, and nutritive signals (Fig. 44.7). Protein "turnover" represents the sum of degradation and synthesis: the balance between them determines net loss (catabolism) or gain (anabolism) of lean tissue.

A prototypical human protein economy is illustrated in Fig. 44.7. Free amino acids that are released by intestinal digestion and traverse the portal vein are subjected to oxidation in the liver or pass to the general circulation. Urinary and biliary excretion of most amino acids is minimal (≤0.01 g/kg•day) and, with regard to net nitrogen balance, can be ignored. The large intracellular protein reservoir (~110 g per kg of body weight) turns over at a rate 3- to

Intracellular protein comprises 10–12% of body mass and undergoes continual synthesis and breakdown ("turnover"). The most volatile and dangerous IEMs are characterized by rapid accumulation of protein-derived cytotoxins during catabolic states.

Biological stress stimulates net rates of protein catabolism between 0.1 g/kg•day (viral infections) and 1.5 g/kg•day (severe burns); this is mirrored by the pace and magnitude of intoxication from protein-derived toxins such as leucine, ammonia, and propionyl-CoA.

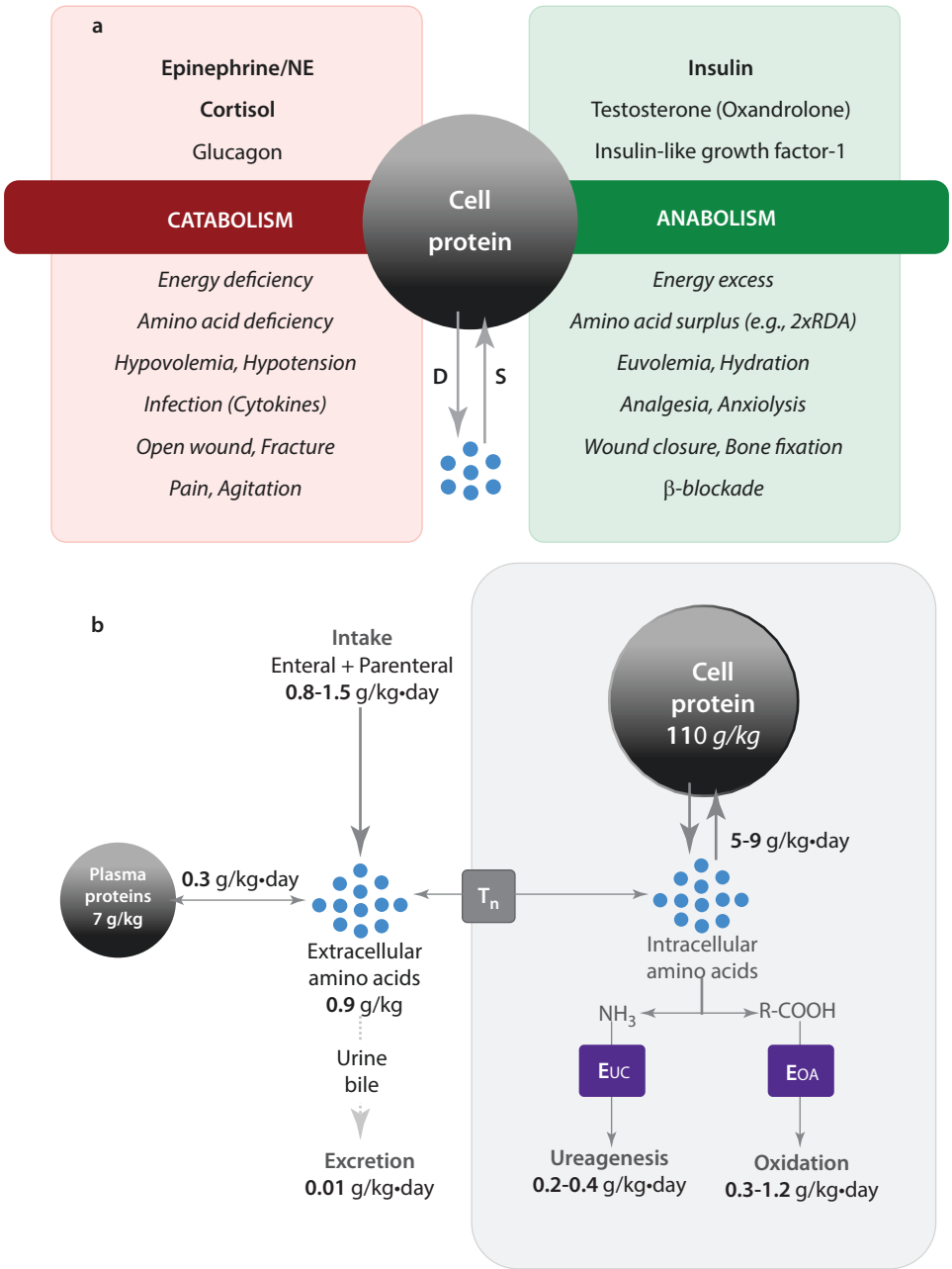

Fig. 44.7 Protein turnover. (**a**) Intracellular protein turnover is the sum of degradation (D) and synthesis (S). Protein-derived toxins (blue circles) increase during catabolic states (D > S). Clinical variables that control protein turnover can be manipulated to reverse metabolic crises. *Abbreviations:* RDA, recommended daily allowance. (**b**) Extracellular and intracellular amino acids (blue circles) traverse membranes via specific transporters (T_n). Some amino acids (~0.3 g/kg•day) exchange with plasma proteins (7 g/kg) via synthesis and degradation, but the largest amino acid reservoir is intracellular protein (110 g/kg body weight; 16% nitrogen), which in children turns over at 5–9 g/kg•day. Amino acid degradation requires oxidation of carboxylic acids (R-COOH; E_{OA}) and disposal of ammonia (NH_3) via the urea cycle (E_{UC}). Metabolic crises arise from defects in these pathways, and the balance between protein synthesis and degradation is reflected in the rate of toxin generation. Urinary and biliary excretions of amino acids are negligible, and under normal conditions dietary protein intake is matched by the sum of amino acid oxidation and new protein accretion

6-fold higher than daily protein intake. Thus, cytotoxins derived from intracellular protein (e.g., ammonia, branched-chain amino acids [BCAAs], mitochondrial acyl-CoA thioesters, and carboxylic acids) can increase rapidly during catabolic states and represent a quantitatively more serious threat than dietary sources.

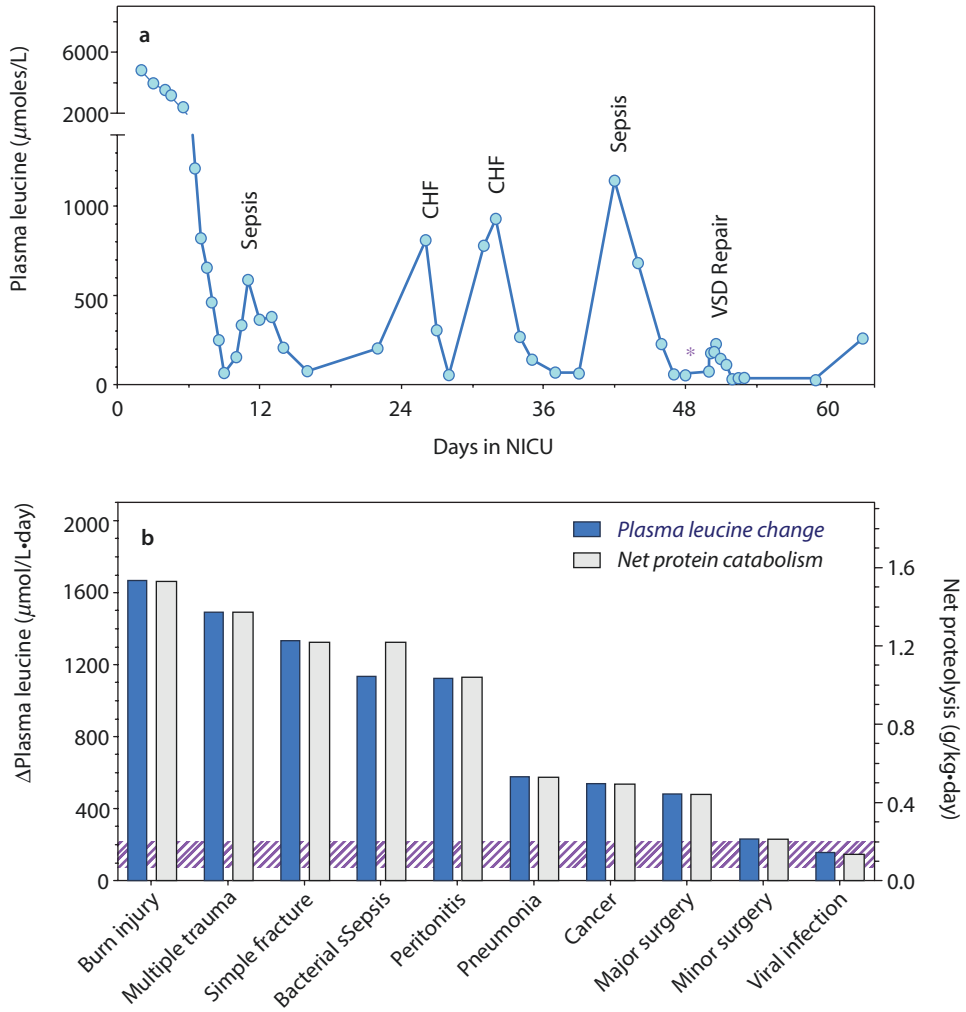

Fig. 44.8 Protein catabolism during illness. (**a**) A neonate with classical maple syrup urine disease (MSUD) and trisomy 21 was hospitalized in the newborn intensive care unit (NICU) for duodenal atresia, ventricular septal defect (VSD), and congestive heart failure (CHF). Fluctuations of plasma leucine concentration (blue circles) mark a series of catabolic stresses and their treatment over a 64-day NICU course. Anticipatory nutritional support (purple asterisk) controlled BCAA catabolism during VSD repair. (**b**) Children with MSUD cannot oxidize branched-chain amino acids, including leucine (MW 131 g/mol), which represents ~10% of tissue protein mass and distributes equally across cell membranes. In the setting of BCAA restriction, leucine ingestion, oxidation, and excretion are negligible, and an increase (Δ) of plasma leucine concentration (blue bars; μmol/L•day, *left axis*) perfectly traces the net balance between protein synthesis and degradation (gray bars; g/kg•day, *right axis*). The purple shaded area represents the plasma reference range for leucine concentration (57–209 μmol/L)

Understanding these relationships allows for accurate predictions about the status of protein turnover during metabolic crises. For example, in children with classical maple syrup urine disease (MSUD; OMIM PS248600), branched-chain keto acid dehydrogenase activity is absent; leucine (MW 131 g/mol) comprises ~10% of tissue protein mass, and intra- and extracellular fluid concentrations of BCAAs are comparable. This simplifies the protein economy in a hospitalized patient on corrective therapy: BCAA ingestion, oxidation, and excretion are negligible in this setting, and therefore changes in plasma leucine concentration perfectly trace the net balance between protein synthesis and degradation (Fig. 44.8).

Similar principles apply to the production and disposition of ammonia. Approximately 16% of protein mass is nitrogen, linking ureagenesis to proteolysis and amino acid oxidation (Fig. 44.7). Urea (MW 60 g/mol) contains two nitrogen atoms derived from ammonia (MW 17 g/mol). Proximal urea

cycle defects (UCDs) impose a massive nitrogen burden during catabolic states. Consider a child with carbamoylase phosphate synthetase 1 (CPS1; OMIM 237300) or ornithine transcarbamylase (OTC; OMIM 311250) deficiency who contracts an invasive bacterial infection and develops a negative protein balance of 0.5–1.0 g/kg•day. Proteolysis rates this high generate between 6000 and 12,000 μmol of NH_3 per 24 hours and can increase blood ammonia concentration 1000–2000 μmol/L per day. Between 75 and 90% of this ammonia partitions to intracellular fluid where it combines with glutamate and CO_2 to form glutamine and glycine, respectively, which increase in proportion to the nitrogen load.

44.2.4 Acid-Base Physiology

44.2.4.1 Organic Acids

Organic acids are partially dissociated at physiological pH, governed by the Henderson-Hasselbalch equilibrium. Clinically relevant organic acids have pK_a values of 3.07–4.88; within this pH range, each one unit increase of urine pH can increase renal clearance 10-fold.

Ammonia base (NH_3) is in reversible equilibrium with ammonium ion (NH_4^+). Only NH_3 (pK_a = 9.14) diffuses freely across the blood-brain barrier; therefore, total brain ammonia relative to plasma increases as blood becomes more alkaline.

A number of IEMs result in formation of organic acid intermediates within mitochondria. Organic acids are partially dissociated at physiological pH; the ratio of negatively charged anion (A^-) to neutral acid (HA) depends on the ionization constant (pK_a) and is represented by the Henderson-Hasselbalch equilibrium:

$$pH = pK_a + \log 10\left(\left[A^- / HA\right]\right)$$

Cell membranes are generally more permeable to an undissociated (uncharged) acid as compared to its corresponding anionic base, and studies of drug distribution show that for most weak acids, back-diffusion from the renal tubular lumen to blood is lowest when the drug is maximally ionized.

This principle can be applied to organic acids. Because pK_a is a logarithmic function, small changes of urine pH markedly effect renal clearance, especially for acids with a pK_a close to physiologic pH. The pK_a of clinically relevant organic acids ranges from 3.07 (methylmalonic) to 4.88 (propionic) and, within this range, each one unit change of urine pH (normal range 5–8) theoretically increases renal clearance 10-fold.

Inter- and intraindividual organic acid excretion rates vary widely among patients. For infants with glutaric acidemia type 1 (GA1; OMIM 231670), urinary glutarate excretion ranges from 1 to 300 μmol/kg•day. In comparison, patients with classical methylmalonic acidemia (MMA; OMIM 251000) excrete 200–1500 μmol/kg•day of methylmalonate. These values represent between 0.001 and 1.0 g/kg•day of degraded protein (◘ Fig. 44.7). Thus, a large proportion of proteolytic intermediates can be recovered as excreted organic acids, and their clearance is maximized by high flow of alkaline urine.

This set of principles underlies the administration of acetate or bicarbonate (e.g., 1–3 mEq/kg•day; titrated to urine pH ≥ 7) to patients with organic acidemias. Few published data address this strategy directly and, although widely practiced, alkalinization is of uncertain clinical value. Importantly, the pathophysiology of organic acidemias appears more closely linked to *intracellular* concentrations of acyl-CoA thioesters and their chemical derivatives; organic acids may simply reflect circulating markers of cellular toxicity. Accordingly, reversing protein catabolism (and intracellular toxin generation) remains more fundamental to treatment than enhancing organic acid excretion.

44.2.4.2 Ammonia

Acid-base chemistry is clinically relevant to the biodistribution of ammonia. Ammonia base (NH_3) is in reversal equilibrium with its charged ammonium ion (NH_4^+), where $pH = pK_a + \log(NH_3/NH_4^+)$, pK_a is 9.14, and 98% of nitrogen is in the form of NH_4^+ at pH 7.40. NH_3 diffuses freely from the blood into the brain but the blood-brain barrier is relatively impermeable to NH_4^+. Due to the relative acidity of brain cells (pH 7.0), total ammonia concentration (NH_3 and NH_4^+) is ~2.5-times higher in brain as compared to blood at physiological pH.

For the intensivist, the important point is that ammonia concentration in brain relative to blood increases as blood becomes more alkaline. For example, increasing blood pH from 7.4 to 7.6 doubles the ammonia concentration gradient between brain and blood. Perversely, hyperammonemia stimulates central ventilatory drive to cause respiratory alkalosis, which increases cerebral ammonia at any given blood level. This can be exacerbated by hyperventilation maneuvers sometimes used to manage cerebral edema in hyperammonemic patients.

44.3 Clinical Presentation

Metabolic crises present to the intensivist in nonspecific ways and notoriously mimic common disease states such as sepsis, shock, and child abuse. Three broad clinical paradigms predominate: (1) an unstable perinatal transition marked by hypoglycemia, metabolic acidosis, hepatopathy, and/or encephalopathy; (2) acute encephalopathy in the setting of a triggering (usually infectious) illness, accompanied by one or more metabolic derangements such as hypoglycemia, metabolic acidosis, hyper- or hypoketosis, lactic acidemia, hyperammonemia, organic acidemia, and/or amino acid dyshomeostasis; or (3) acute organ injury or failure, such as metabolic stroke, dilated cardiomyopathy, hepatopathy, rhabdomyolysis, or pancreatitis, with or without signs of metabolic decompensation.

Knowledge of these paradigms is useful but can be misleading when applied to individual cases. For example, galactosemia (OMIM 230400) classically manifests as hypoglycemia, hepatopathy, and encephalopathy in a breastfeeding neonate but may first present to the intensivist as hyperbilirubinemia, coagulopathy, or *Escherichia coli* sepsis. Young patients with propionic acidemia (PPA; OMIM 606054) often present with attacks of hypoglycemia, ketoacidosis, hyperammonemia, and hyperglycinemia accompanied by elevations of propionylcarnitine and various organic acids in body fluids, but these same patients can present later in life with dilated cardiomyopathy or acute pallidal necrosis in the absence of metabolic acidosis. Glutaric acidemia type 1, although categorized as an organic acidemia, seldom manifests as episodic metabolic decompensation. More often, infants with GA1 present with acute striatal necrosis in the setting of illness and have no signs of biochemical instability.

Fortunately, such diagnostic mysteries are rare in the modern era. Most serious metabolic defects are detected by tandem mass spectrometry (MS/MS), which now represents the standard for newborn screening in the majority of US states and developed countries. MS/MS technology generates both an amino acid and acylcarnitine profile from dried filter paper blood spots, consolidating the detection of amino acid, fatty acid, and organic acid disorders to a single analytical platform. The full MS/MS panel of acylcarnitines and amino acids (~20 individual analytes) yields an IEM diagnosis in approximately 1 per 4000 newborns (■ Table 44.2). Accordingly, diagnostic evaluation for a suspected IEM begins with a call to the newborn screening laboratory to (1) verify that MS/MS screening was performed, (2) review analyte results,

Metabolic crises notoriously mimic more common disease states such as sepsis, shock, and child abuse. Paradigms particularly suggestive of an IEM include precipitous deterioration of a previously healthy newborn, acute encephalopathy in the setting of a triggering illness, or sudden and unexplained organ dysfunction or injury.

Patients with propionic, methylmalonic, or isovaleric acidemia typically suffer recurrent attacks of ketoacidosis during infancy and early childhood, but these same patients can present later in life with dilated cardiomyopathy, renal insufficiency, or acute pallidal necrosis.

Most serious metabolic defects are diagnosed by tandem mass-spectrometry-based newborn screening, which detects amino acid, fatty acid, and organic acid disorders using a single analytical platform.

Certain IEMs mimic child abuse; e.g., retinal and subdural hemorrhages are rare signs of glutaric acidemia type 1, and hereditary hypercholanemias cause vitamin-K-responsive coagulopathy that can result in spontaneous intracranial bleeding.

Table 44.2 Inborn errors of metabolism commonly diagnosed by MS/MS-based newborn screening

Inborn error of metabolism	MS/MS Analyte(s)	Gene(s)	OMIM number(s)
Amino acid and urea cycle disorders			
Maple syrup urine disease	Leu+Iso, Val	*BCKDHA, BCKDHB, DBT*	248600
Phenylketonuria	Phe	*PAH*	261600
Cystathionine β-synthase deficiency	Met	*CBS*	236200
Hypermethioninemia	Met	*MAT1A, AHCY, ADK*	250850, 613752, 614300
Citrullinemia	Cit	*ASS1, SLC25A13*	603470, 605814
Argininosuccinic aciduria	Cit	*ASL*	608310
Tyrosinemia type 1	Tyr	*FAH*	276700
Tyrosinemia type 2	Tyr	*TAT*	276600
Argininemia	Arg	*ARG1*	207800
Glycine encephalopathy	Gly	*AMT, GLDC, GCSH*	605899
Hyperammonemia-ornithinemia-citrullinemia	Orn, Homocit	*SLC25A15*	238970
5-oxoprolinuria, pyroglutamic aciduria	5-Oxopro	*GSS*	266130
Fatty Acid Oxidation Disorders			
Short-chain acyl-CoA dehydrogenase deficiency	C4	*ACADS*	201470
Medium-chain acyl-CoA dehydrogenase deficiency	C8, C10, C10:1, C6	*ACADM*	201450
Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency	C16OH, C18:1OH, C18OH	*HADHA*	609016
Very long-chain acyl-CoA dehydrogenase deficiency	C14:1, C14, C16	*ACADVL*	201475
Multiple acyl-CoA dehydrogenase deficiency (GA2)	C4, C5, C8:1, C8, C16, C5DC, etc.	*ETFDH, ETFA, ETFB*	231680
Mitochondrial trifunctional protein deficiency	C16OH, C18:1OH, C18OH	*HADHA, HADHB*	609015
Carnitine-acylcarnitine translocase deficiency	C16, C18:1, C18	*SLC25A20*	212138
Carnitine palmitoyl transferase type 1 deficiency	C16, C18:1, C18 (low)	*CPT1A*	255120
Carnitine palmitoyl transferase type 2 deficiency	C16, C18:1, C18	*CPT2*	600650

Table 44.2 (continued)

Inborn error of metabolism	MS/MS Analyte(s)	Gene(s)	OMIM number(s)
Organic Acid Disorders			
Propionic acidemia	C3	*PCCA, PCCB*	606054
Methylmalonic acidemia	C3	*MUT*	251000
Cobalamin C defects	C3	*MMAHC, PRDX1*	277400
Isovaleric acidemia	C5	*IVD*	243500
Glutaric acidemia type 1	C5DC	*GCDH*	231670
3-hydroxy-3-methylglutaryl-CoA lyase deficiency	C5OH	*HMGCL*	246450
3-methylcrotonyl-CoA carboxylase deficiency	C5OH	*MCCC1*	210200
Malonic-methylmalonic acidemia	C3DC	*ACSF3*	614265
Isobutyrl-CoA dehydrogenase deficiency	C4	*ACAD8*	611283
Alpha-methylacetoacetic acidemia	C5:1, C5OH	*ACAT1*	203750
2-methyl-3-hydroxybutyrl-CoA dehydrogenase deficiency	C5:1, C5OH	*HSD17B10*	300438

Notes and Abbreviations: Tandem mass spectrometry (MS/MS) expertise and diagnostic cutoffs vary by laboratory. The MS/MS platform generates both an amino acid and acylcarnitine profile. In the analyte column, amino acids are listed using their standard three-letter abbreviations. Abbreviations for acylcarnitines are based on the number of carbons (e.g., C5 is a 5-carbon acylcarnitine ester), and indicate the presence of an unsaturated bond (:1), hydroxyl group (OH), or dicarboxylic acid structure (DC)

and (3) determine which relevant IEMs were *not* screened by the panel employed (Table 44.3).

When newborn screening results are not available, clinical history, physical examination, screening laboratories, and imaging results can provide important clues. Certain symptoms and signs are particularly suggestive of an IEM (Tables 44.4 and 44.5):

- Congenital, medically intractable seizures
- Acute, unexplained illness in a previously healthy neonate, especially when accompanied by hypoglycemia, ketosis, or hyperammonemia
- Clinical signs of septicemia in an infant or young child with no laboratory evidence of infection
- Postprandial or fasting hypoketotic hypoglycemia in individuals of any age
- Recurrent episodes of vomiting, dehydration, or encephalopathy provoked by intercurrent illness and/or prolonged fasting
- Global or isolated motor delay without known cause
- Unexplained regression, spasticity, or movement disorder ("pseudo"cerebral palsy)
- Unexplained organ injury or failure in the setting of biological stress, e.g., symmetric gray matter necrosis, dilated or hypertrophic cardiomyopathy,

Table 44.3 Selected inborn errors of metabolism *not* detected by MS/MS newborn screening

Inborn error of metabolism	Presenting sign(s)	Gene(s)	OMIM number(s)
Glycogen storage disorders	Hypoglycemia, lactic acidemia, (cardio) myopathy	e.g., *GCPC*, *AGL*, etc.	232200, 232400, etc.
Familial hyperinsulinemia	Hypoketotic hypoglycemia	e.g., *ABCC8*, *GCK*, etc.	PS256450
Proximal urea cycle disorders	Hyperammonemia	e.g., *CPS1*, *OTC*, etc.	237300, 311250, etc.
Crigler-Najjar syndrome	Hyperbilirubinemia	*UGT1A1*	218800
Hereditary fructosemia	Hypoglycemia, hepatopathy	*ALDOB*	229600
Familial hypercholanemia	Vitamin-K-dependent coagulopathy	*TJP2*, *BAAT*, *EPHX1*	607748
Cerebral GLUT1 deficiency (neuroglycopenia)	Epilepsy, dystonia	*SLC2A1*	606777
Pyridoxine-dependent epilepsy	Intractable epilepsy (B6-responsive)	*ALDH7A1*	266100
Pyridoxine 5'-phosphate oxidase deficiency	Intractable epilepsy (5'-B6-responsive)	*PNPO*	610090
Molybdenum cofactor deficiency	Intractable epilepsy, dystonia, hypotonia	*MOCS1*, *MOCS2*, *GPHN*	252160, 615501
Cerebral folate transporter deficiency	Epilepsy, developmental regression	*FOLR1*	613068
Cerebral creatine deficiency syndrome	Hypotonia, developmental delay, seizures	*SLC6A8*, *GAMT*, *GATM*	PS300352
Sulfite oxidase deficiency	Dystonia, hypotonia, encephalopathy	*SUOX*	272300
Aromatic L-amino acid decarboxylase deficiency	Dystonia, oculogyric crisis (DOPA-responsive)	*DDC*	608643
Segawa syndrome	Dystonia, oculogyric crisis (DOPA-responsive)	*TH*, *GCH1*	605407, 128230
Dopamine transporter deficiency	Dystonia, rigidity (DOPA-*non*responsive)	*SLC6A3*	613135

fasting rhabdomyolysis, hepatopathy, nonobstructive pancreatitis, or renal tubulopathy

Physical anomalies, especially when coupled with distinctive laboratory or imaging findings, can signal an IEM. Classic examples include macrocephaly and symmetric middle cranial fossae fluid collections in GA1; lens dislocations associated with cystathionine β-synthetase (OMIM 236200), sulfite oxidase (OMIM 272300), or molybdenum cofactor (OMIM PS252150) deficiencies; and the constellation of dysmorphic features and laboratory findings associ-

Table 44.4 Clinical clues to an inborn error of metabolism

History	*Physical findings*
Unstable neonatal transition	Dysmorphic or coarse facial features
History of perinatal apnea or irregular breathing	Lethargy, stupor, or coma
Failure to thrive	Micro- or macrocephaly
Recurrent or intractable vomiting	Distinctive body odor
Recurrent hypoglycemia or ketoacidosis	Cataracts
Illness triggered by ingestion of certain foods	Ectopia lentis
Unexplained developmental delay	Pigmentary retinopathy
Acute motor regression	Ambiguous genitalia
Unsubstantiated "pseudo" cerebral palsy	Skeletal abnormalities
Dystonia, chorea, spasticity, or ataxia	Skin and/or hair abnormalities
Intellectual disability	Signs of cardiomyopathy
Seizures, especially if intractable	Hepatomegaly
Hearing or vision impairment	Jaundice
Unexplained cardiomyopathy	Unexplained ecchymosis
Recurrent rhabdomyolysis or pancreatitis	Low muscle mass (especially lower limbs)
Unexplained bruising or internal bleeding	Flaccid paralysis
Family history of unexplained death or metabolic illness	Dystonia, chorea, dyskinesia, rigidity, spasticity, or ataxia
Parental consanguinity or high-risk ancestry	
Laboratory results	*Functional studies*
Hypoglycemia	Diffuse cerebral edema
Hypoketosis	Symmetric cytotoxic edema of basal ganglia nuclei
Hyperketosis	Slow, disorganized electroencephalographic background
Metabolic acidosis	Epileptiform electroencephalogram
Hyperammonemia	Dilated or hypertrophic cardiomyopathy
Unconjugated or conjugated hyperbilirubinemia	Unexplained renal tubulopathy or insufficiency
Vitamin-K-responsive or nonresponsive coagulopathy	Renal cysts
Lactic acidosis	
Elevated liver transaminases (ALT, AST)	
Elevated cardiac enzymes (CK-MB, troponin I, pro-BNP)	
Elevated muscle enzymes (CK, aldolase)	
Elevated pancreatic enzymes (lipase, amylase)	

Table 44.5 Neonatal "red flags"

Poor feeding
Hypoglycemia
Ketones in urine
Hepatopathy
Unconjugated hyperbilirubinemia
Cholestasis
Unexplained coagulopathy
Escherichia coli septicemia
Apnea or irregular respirations
Opisthotonic posturing
"Fencing" posture or "bicycling" movements
Lethargy, stupor, coma

For any child with a suspected IEM, the diagnostic evaluation should commence with a systematic collection of key laboratory specimens followed by a call to the state newborn screening laboratory.

For children on therapies that can mask metabolic disease expression (e.g., glucose infusion), earlier ("presenting") samples held at the core clinical laboratory are sometimes informative.

Hyperammonemia coincides with *respiratory alkalosis* in urea cycle disorders versus *metabolic acidosis* in organic acidemias; hypoglycemia coincides with *hyperketosis* in organic acidemias versus *hypoketosis* in disorders of fatty acid oxidation and insulin regulation.

For many IEMs, standard biochemical measures (e.g., glucose, electrolytes, ammonia, osmolality, etc.) are sufficient to gauge disease severity and guide treatment.

For children with reversible cerebral edema, stringent control of serum osmolality is the key to preventing catastrophic herniation or stroke until metabolic intoxication subsides.

Cerebrospinal fluid examination is diagnostic of several rare but treatable IEMs, including defects of blood-brain glucose transport, neurotransmitter synthesis, pyridoxine metabolism, and cerebral folate uptake.

ated with lysosomal storage disorders (OMIM PS607014), Smith-Lemli-Opitz syndrome (OMIM 270400), congenital glycosylation defects (OMIM PS212065), glutaric acidemia type 2 (OMIM 231680), disorders of peroxisome biogenesis (OMIM PS214100), and Menkes disease (OMIM 309400). However, most IEMs have no physical phenotype, and laboratory data are the bedrock of diagnosis and management.

44.4 Laboratory Studies

Any acutely ill child suspected to have an IEM should have laboratory testing at the earliest opportunity (Table 44.6), before metabolic derangements such as hyper- or hypoketosis are masked by clinical interventions. Most core laboratories retain biological specimens for hours or days after collection. Thus, for a child on therapy that attenuates disease expression (e.g., fluid, glucose, or bicarbonate infusion), "presenting" samples, e.g., those collected in an emergency department, may prove critical to diagnosis. Analyzing metabolic variables in combination can refine the differential diagnosis. As a classic example, hyperammonemia is coupled to metabolic acidosis in organic acidemias versus respiratory alkalosis in UCDs. Similarly, hypoglycemia coincides with ketoacidosis in organic acidemias as compared to hypoketosis in disorders of fatty acid oxidation or insulin regulation.

Esoteric metabolites are important for managing certain IEMs (e.g., MSUD), but practical management is usually focused on standard biochemical measures like glucose, bicarbonate (total CO_2), anion gap, β-hydroxybutyrate, ammonia, osmolality, and electrolytes, which are often sufficient to indicate disease severity and guide corrective therapy. For example, during an acute ketoacidotic crisis characteristic of PPA, changes in serum concentrations of glucose, total CO_2, anion gap, and β-hydroxybutyrate reliably track the illness and its resolution (Fig. 44.9). When a child with a UCD or MSUD presents with critical brain edema, careful management of serum osmolality is key to preventing a neurological catastrophe.

Reversible hepatopathy is a feature of several IEMs, and children with galactosemia or hereditary hypercholanemia (OMIM 607748) are sometimes coagulopathic (Table 44.7). Hypercholanemias (Table 44.3) cause insidious

Table 44.6 Minimal laboratory evaluation for suspected inborn error of metabolism

Laboratory test	Specimen
Complete blood count	Whole blood
Blood gases[a]	Whole blood
Prothrombin and partial thromboplastin times[b]	Whole blood
DNA specimen (hold for further testing)	Whole blood
Glucose and electrolytes	Serum
Phosphorus	Serum
Uric acid	Serum
Osmolality (and osmolar gap)[c]	Serum
Liver enzyme panel	Serum
Bilirubin, total and direct	Serum
Creatine kinase, aldolase	Serum
Cardiac enzyme panel	Serum
Lipase, amylase	Serum
β-hydroxybutyrate	Serum, plasma
Lactate[d]	Serum, plasma
Ammonia	Serum, plasma
Amino acids	Plasma
Acylcarnitines	Plasma, urine
Organic acids	Urine
Urinalysis	Urine
Hold (freeze) acute specimens for later studies	Urine, plasma, serum

[a]Some point-of-care devices measure lactate and glucose concentrations in parallel with blood gases
[b]Hereditary hypercholanemias can cause insidious vitamin-K-responsive coagulopathy, which is detected using a test for proteins induced by vitamin K absence (PIVKA-II, a.k.a. des-γ-carboxyprothrombin).
[c]Osmolar gap is the difference between measured osmolality and calculated osmolarity (O_c, in mmol/L), where
O_c = ([Na + K] x 2) + (Glu/18) + (U/2.8). Serum sodium (Na) and potassium (K) concentrations are expressed in mmol/L, glucose (Glu) and urea (U) concentrations are in mg/dL, and the difference between units of measurement for osmolality (mOsm/kg H2O) and osmolarity (mOsm/L) is considered negligible. The normal osmolar gap is <10 mOsm/L
[d]Plasma lactate specimens should be placed on ice at the bedside and quickly separated from red blood cells, which are a common source of artefactually elevated lactate concentrations

vitamin-K-responsive coagulopathy that can result in spontaneous intracranial hemorrhage easily mistaken for child abuse. A relatively esoteric test for proteins induced by vitamin K absence (PIVKA-II, a.k.a. des-γ-carboxyprothrombin) is useful for specifically attributing coagulopathy to vitamin K deficiency. Accordingly, when an IEM is suspected but the diagnosis is unknown, we recommend a survey for organ system injury that includes liver, cardiac, skeletal muscle, and pancreatic enzyme panels and, when indicated, prothrombin time, partial thromboplastin time, and PIVKA-II (Tables 44.6 and 44.7).

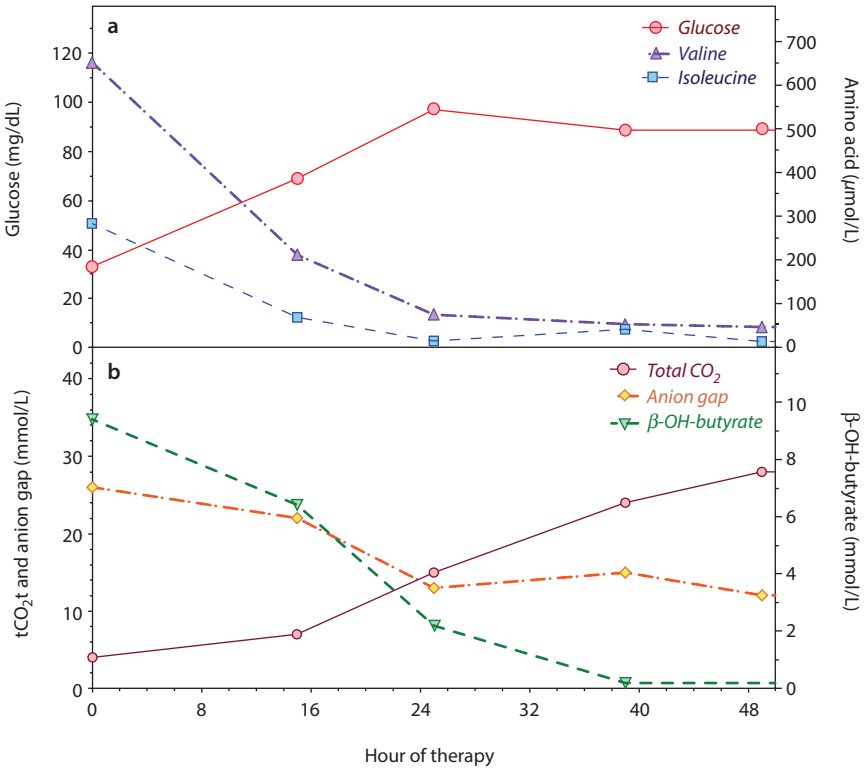

Fig. 44.9 Propionic acidemia; resolution of ketoacidotic crisis. A 3-year-old boy with biallelic mutations in the *PCCB* gene presented with hypoglycemic ketoacidosis triggered by viral gastroenteritis. Over a 50-hour hospital course, he was treated with 1.5-times maintenance fluid, dextrose (10 mg/kg•min), bicarbonate (2 mEq/kg•day), intravenous L-carnitine (400 mg/kg•day), and a specialized amino acid mixture devoid of isoleucine and valine. (**a**) Serum glucose concentration (red circles) stabilized as plasma isoleucine (blue squares) and valine (purple triangles) concentrations decreased. (**b**) Metabolic acidosis resolved in parallel, marked by an increase of serum total CO_2 (maroon circles) and decreases of β-hydroxybutyrate (green triangles) and anion gap (orange diamonds)

Certain diagnoses require cerebrospinal fluid (CSF) examination. Children with defects of cerebral glucose transport (SLC2A1; OMIM 606777) have CSF glucose (16.2–50.5 mg/dL [0.9–2.8 mmol/L]) and CSF lactate (5.4–13.5 mg/dL [0.6–1.5 mmol/L]) concentrations below the tenth percentile for age, with a ratio of CSF to blood glucose ranging from 0.19 to 0.59. Analysis of CSF monoamine neurotransmitters, pterins, and folic acid metabolites can reveal several exceedingly rare but treatable disorders, including tyrosine hydroxylase (TH; OMIM 605407) and aromatic L-amino acid decarboxylase (DDC; OMIM 608643) deficiencies, pyridoxine-dependent epilepsy (ALDH7A1; OMIM 266100), and cerebral folate transporter deficiency (FOLR1; OMIM 613068).

44.5 Neuroimaging

Neuroimaging has diagnostic and prognostic value in certain contexts. Intoxicated MSUD patients have a combination of cytotoxic and vasogenic brain edema that can culminate in stroke or cerebral herniation (Table 44.7; Fig. 44.10). A similar pattern of diffuse cerebral brain edema accompanies hyperammonemia and appears linked to the distribution of ammonia across the blood-brain barrier and its condensation with glutamate to form glutamine in astrocytes (Fig. 44.11). The cytotoxic edema of MSUD and hyperammonemic encephalopathy is fully reversible.

In contrast, focal, symmetric cytotoxic edema of subcortical neurons is an ominous prognostic sign in patients with organic acidemias (e.g., GA1, PPA, MMA) and heralds irreversible and often devastating "metabolic stroke" of extrapyramidal ganglia (Fig. 44.10). For reasons that remain obscure, such injuries are most common during (and might be restricted to) the first few years of life. Their anatomical distribution varies according to the specific enzyme defect, e.g., brain injury in GA1 is confined to medium spiny neurons

Encephalopathic patients with maple syrup urine disease or hyperammonemia have diffuse, *reversible* cerebral edema, whereas sudden regression of an infant or toddler with an organic acidemia often heralds *irreversible* "metabolic stroke" of basal ganglia nuclei.

The brain injury of glutaric acidemia type 1 is confined to medium spiny neurons of the putamen and caudate nucleus. Pallidal neurons are preferentially affected in propionic and methylmalonic acidemias.

Proton magnetic resonance spectroscopy has diagnostic applications for disorders of pyruvate dehydrogenase complex and the respiratory chain, glycine encephalopathies, disorders of creatine synthesis and transport, and maple syrup urine disease.

Table 44.7 Recognition and treatment of comorbidities associated with inborn errors of metabolism

Comorbidity	Representative disorders	Representative gene(s)	Clinical considerations
Cerebral edema	Maple syrup urine disease	*BCKDHA, BCKDHB, DBT*	Elevate head
	Urea cycle disorders	*NAGS, CPS1, OTC*	Avoid prolonged hyperventilation
			Maintain euvolemia, normotension, normoxemia, and euglycemia
			Prevent fluctuation (decreases) of serum osmolality
			Hypertonic (3%) saline, mannitol, and furosemide *as needed*
			Consider neurosurgery consult (e.g., CSF drainage, ICP monitoring)
Cardiomyopathy	Propionic acidemia	*PCCA, PCC*	*Echocardiography:* chamber morphology, performance, diastology
	Glycogen storage disease type 2 (Pompe disease)	*GAA, GBE1, GLA, AGL, PRKAG2*	*Electrocardiography*: LV voltages, QT_c interval, preexcitation, arrhythmias
	Glycogen storage disease type 5 (McArdle disease)	*PYGM*	Monitor for clinical signs of congestive heart failure
	Disorders of (very) long-chain fatty acid oxidation	*ACADVL, HADHA, HADHB*	Employ standard hemodynamic and cardioprotective therapies
	Mitochondrial disorders (e.g., MELAS, Leigh syndrome)	See OMIM: 540000, 256000	Monitor pro-BNP and myocardial enzymes (CK-MB, troponin I)
	Mitochondrial adenine nucleotide exchanger (ANT1)	*SLC25A4*	
	Barth syndrome	*TAZ*	
	Friedrich ataxia	*FXN*	
	Tyrosinemia type 1	*FAH*	

(continued)

Table 44.7 (continued)

Comorbidity	Representative disorders	Representative gene(s)	Clinical considerations
Rhabdomyolysis	Disorders of (very) long-chain fatty acid oxidation	*ACADVL, HADHA, HADHB*	Volume infusion at 1.5- to 2-times maintenance
	Carnitine palmitoyl transferase 2 deficiency	*CPT2*	Bicarbonate infusion to achieve urine pH ≥6.5
	Systemic carnitine deficiency	*SLC22A5*	Monitor muscle enzymes (aldolase, CK)
Hepatopathy	Galactosemia	*GALT*	Treat clinical or laboratory signs of coagulopathy
	Fructose intolerance	*ALDOB*	Monitor liver transaminases (ALT, AST)
	Disorders of (very) long-chain fatty acid oxidation	*ACADVL, HADHA, HADHB*	Monitor liver synthetic function (albumin, PT, PTT, bilirubin, ammonia)
	Glycogen storage disorders	*G6PC, AGL*	*Hepatobiliary imaging:* cirrhosis, portal hypertension
	Tyrosinemia type 1	*FAH*	
	Maple syrup urine disease	*BCKDHA, BCKDHB, DBT*	
	Organic acidemias	e.g,. *PCCA, PCCB, MUT*	
	Familial hypercholanemias	*TJP2, BAAT, EPHX1*	
Pancreatitis	Hereditary hyperlipoproteinemias	*LPL, APOC*	Optimize hydration
	Organic acidemias	e.g., *PCCA, PCCB, MUT*	Provide appropriate analgesia
	Homocystinuria	*CBS*	Monitor blood glucose
	Mitochondrial disorders	Multiple	Judicious, low-fat enteral feeding as tolerated
Nephropathy	Classical methylmalonic acidemia	*MUT*	Monitor serum creatinine
	Cobalamin C disorders	*MMACHC, PRDX1*	Monitor for hypertension, hyperkalemia, and acidosis
	Tyrosinemia type 1	*FAH*	GFR-specific drug dosing

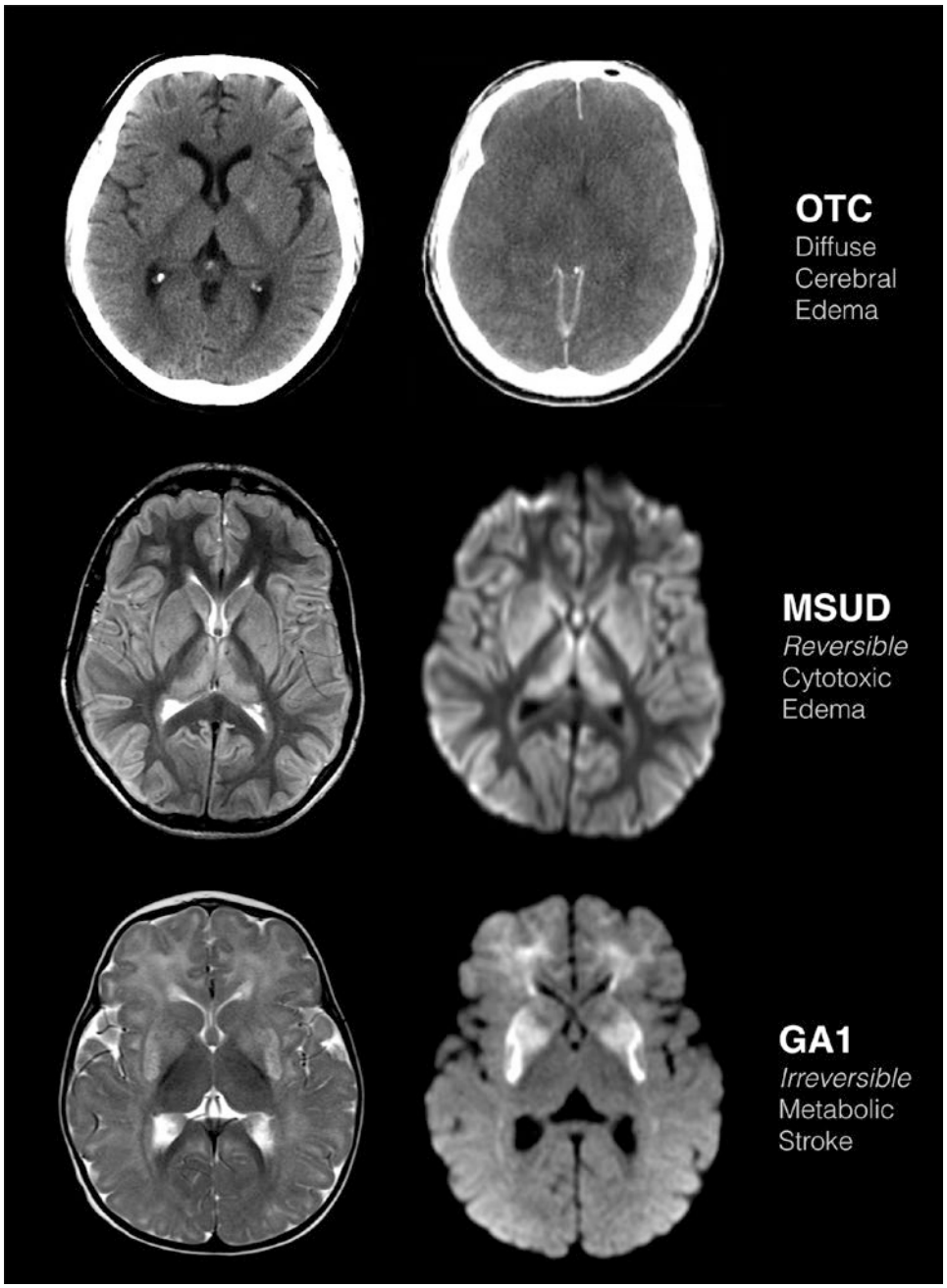

Fig. 44.10 Neuroimaging of acute metabolic encephalopathies. *Upper panels:* A normal cranial CT scan (left) is compared to the severe generalized cerebral edema caused by hyperammonemic encephalopathy in a comatose infant with X-linked ornithine transcarbamylase deficiency (OTC). *Middle panels:* Acute, cytotoxic, and diffuse gray matter edema is characteristic of MSUD encephalopathy represented here on T2 (left) and diffusion-weighted (right) MRI sequences. It is fully reversible. *Lower panels:* An 8-month-old child with glutaric acidemia type 1 presented with sudden motor regression in the setting of gastroenteritis; T2 (left) and diffusion-weighted (right) images show acute cytotoxic edema of the putamina (lentiform nuclei) and reflect irreversible necrosis of medium spiny neurons ("metabolic stroke")

of the striatum (a.k.a. lentiform nucleus) whereas GABAergic pallidal neurons appear preferentially vulnerable in PPA and MMA.

Proton magnetic resonance spectroscopy is clinically useful for measuring brain lactate (disorders of the pyruvate dehydrogenase complex [OMIM PS312170] and respiratory chain), glycine (glycine encephalopathy; OMIM 605899), creatine (cerebral creatine deficiency; OMIM PS300352), and

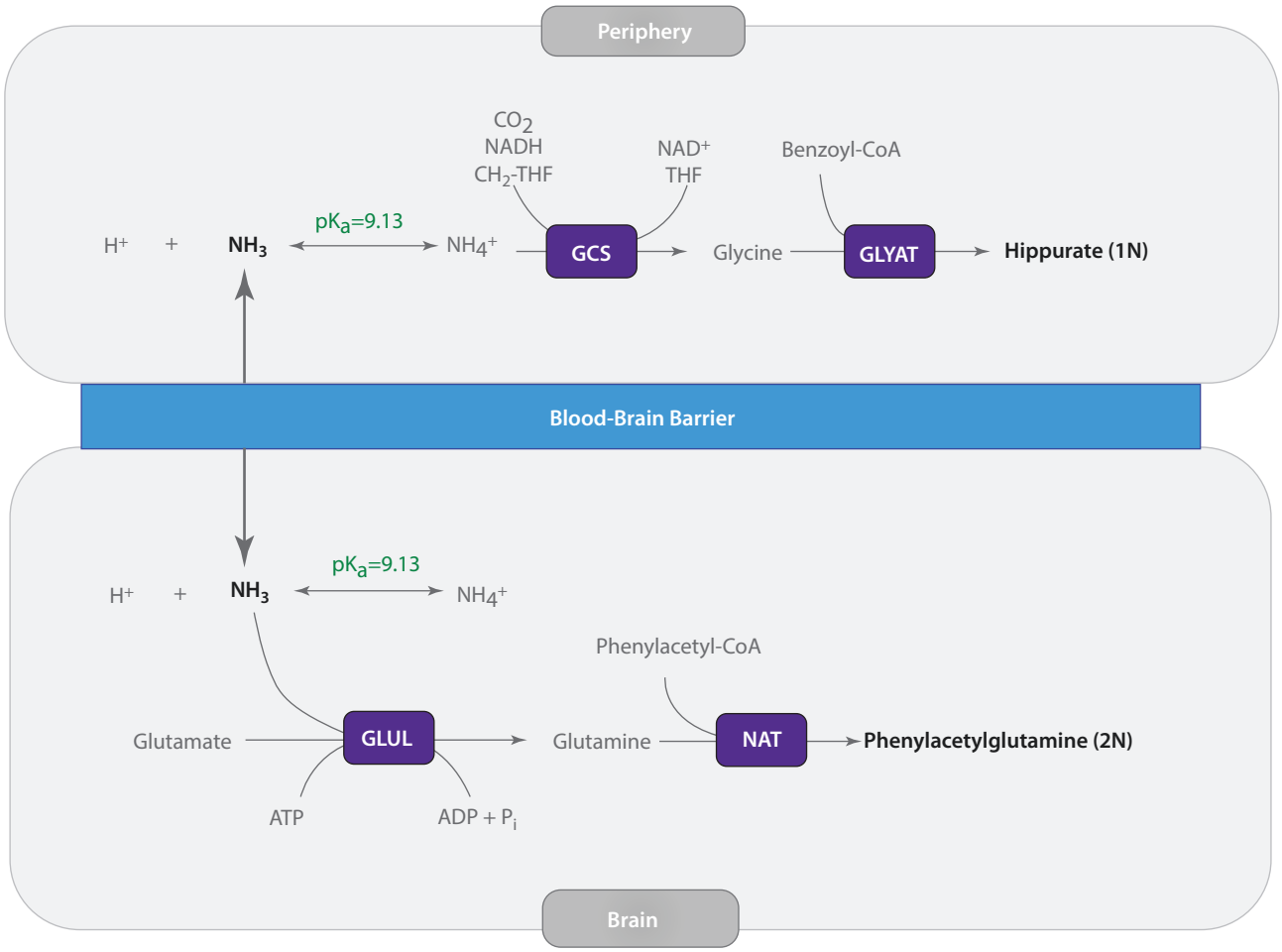

Fig. 44.11 Clinically relevant aspects of ammonia distribution and metabolism. Ammonia base (NH_3) is in reversible equilibrium with its charged ammonium ion (NH_4^+), where pH = pKa + log(NH_3/NH_4^+), pK_a = 9.14, and 98% of nitrogen is in the form of NH_4^+ at pH 7.40. NH_3 diffuses freely across the blood-brain barrier whereas NH_4^+ does not, and thus cerebral ammonia uptake increases as blood becomes more alkaline. Ammonia encephalopathy is linked to its condensation with glutamate to form glutamine in astrocytes (GLUL; glutamate-ammonia ligase). In peripheral tissues, excess $NH4^+$ is incorporated into glutamine as well as glycine (GCS; glycine cleavage system), which combine with the nitrogen scavengers sodium phenylacetate and sodium benzoate to form excretable phenylacetylglutamine and hippurate, respectively (GLYAT; glycine-N-acyltransferase) [Enzymes are labeled using standard protein nomenclature (▶ http://omim.org)]

branched-chain ketoacid (MSUD) concentrations. The full spectrum of neuroradiological changes associated with IEMs is beyond the scope of this chapter, but the subject of excellent reviews by Barkovich and colleagues (2007, 2018) listed among "Suggested Readings."

44.6 Treatment

44.6.1 Evidence and Practice

The majority of children in metabolic crisis first present to an emergency department or PICU where they might encounter clinicians unfamiliar with specific aspects of IEM therapy. It is, therefore, advisable for specialists to furnish families with a standard "emergency letter" or treatment protocol that facilitates the initial steps of therapy. Such documents should be succinct but sufficiently detailed to be useful for treating clinicians and pharmacy staff; relevant specifics might include glucose infusion rates, dosages for L-carnitine or

For any child with an IEM, a specialist should provide families with a standard treatment protocol that is entered into the electronic health record and readily accessible to inpatient pharmacists and clinical providers.

Most interventions for IEMs lack a strong evidence base and instead are based on a combination of physiological reasoning, expert opinion, and individual experience.

nitrogen scavengers, or guidelines for protein and medical formula intake. Standard treatment protocols can be entered into the electronic health record so they are readily accessible to inpatient providers.

Prespecified protocols provide a useful starting point, but most interventions for IEMs lack a strong evidence base. Faced with an acutely ill child in metabolic crisis, the intensivist must rely on some combination of physiological insight, expert opinion, and individual experience. The reasons for this are straightforward. Volatile and dangerous IEMs are rare and, in the era of MS/MS-based newborn screening, metabolic crises are rarer still. It is, therefore, difficult if not impossible to assemble experimental cohorts of statistically meaningful size to compare interventions. For example, unstable CPS1, OTC, and MSUD arguably represent the most complex and dangerous paradigms in metabolic medicine, but most intensivists will never encounter a case. Moreover, such children often present *in extremis*, precluding their assignment to an experimental or placebo arm.

This represents a seemingly insurmountable barrier to generating high-quality evidence in support of particular therapies, a fact which separates treatment of metabolic crises from other aspects of critical care medicine. The recommendations presented here are no different; they are based largely upon individual experience and, where applicable, available clinical data. Accordingly, management recommendations below are intended as a guide only, to be modified and improved in light of new evidence.

44.6.2 Treatment Paradigms

A variety of systems are used to partition IEMs into clinically useful paradigms. Such classification is intrinsically difficult, involves both overlap and redundancy, and leaves some important disorders in search of a category. Nevertheless, most IEMs conform to a few patterns that inform treatment (◘ Table 44.8): (1) congenital epileptic encephalopathy; (2) congenital energy deficiency; (3) hyper- or hypoketotic hypoglycemia; (4) intoxicating encephalopathy; (5) focal neuronal necrosis (metabolic stroke); and (6) dilated or hypertrophic cardiomyopathy. These categories help the clinician orient to a bewildering landscape and set priorities for clinical management.

Categorizing an IEM into one of several discrete clinical paradigms helps to clarify treatment priorities. Intoxicating encephalopathies, especially maple syrup urine disease and disorders of ureagenesis, require the most complex and specific therapy.

Intoxicating encephalopathies require the most complex and specific therapy and receive special attention here. Defects of BCAA degradation (◘ Fig. 44.12) and ureagenesis (◘ Fig. 44.13) predominate in this group. Degradation pathways for the three essential BCAAs (leucine, isoleucine and valine) begin with two common steps – reversible transamination followed by irreversible oxidative decarboxylation – and converge on 2-carbon (acetyl-CoA) and 3-carbon (propionyl-CoA) intermediates that enter the TCA cycle.

Organic acidemias are characterized by accumulation of small, nonmetabolizable, and potentially toxic acyl-CoA thioesters in mitochondria which react with L-carnitine to produce unconjugated CoA and a corresponding acylcarnitine that can be excreted in urine or bile.

MSUD occupies a special position in the scheme, being the only IEM for which both an amino acid (leucine) and ketoacid (α-ketoisocaproic acid) exert significant neurotoxicity. Neonates with classical (severe) variants of MSUD appear healthy at birth, but without specific therapy, progress through a series of clinical stages:

- *12–24 hours*: Elevated plasma concentrations of BCAAs, ketoacids, and allo-isoleucine
- *2–3 days*: Irritability, poor feeding, and ketonuria; maple syrup odor of urine and cerumen
- *4–6 days*: Lethargy, apnea, and opisthotonus; "fencing" and "bicycling" movements
- *7–10 days*: Cerebral edema, coma, and central respiratory failure

Severe deficiency of proximal urea cycle enzymes results in the triad of hyperammonemia, deep encephalopathy, and respiratory alkalosis within days of life.

Table 44.8 Clinical categorization for inborn errors of metabolism: phenotypes, metabolic systems, and clinical priorities

Clinical category	Metabolic pathways	Clinical priorities
Congenital epileptic encephalopathy	Pyridoxine dependence	Rapid diagnosis
(*Medically intractable*)	Pyridoxine 5'-phosphate dependence	Vitamin cofactor supplementation
	Glycine cleavage system	Supportive care
Congenital energy deficiency	Pyruvate dehydrogenase	Diagnose *treatable* conditions (e.g., GLUT1, GAMT, etc.)
(*Lactic acidemia*)	Oxidative phosphorylation	Creatine supplementation as indicated (creatine deficiency)
	Mitochondrial disorders	Ketogenic diet as indicated (e.g., GLUT1 syndrome)
	Cerebral glucose transport	Supportive care
	Creatine metabolism and transport	
Hypoglycemia (± hypoketosis)	Glycogenolysis	Correct hypoglycemia
(± *hepatopathy, rhabdomyolysis, cardiomyopathy*)	Gluconeogenesis	Dextrose infusion to match or exceed EGPR
	Fatty acid oxidation	Identify/treat precipitating stress
	Carnitine transport	Treat L-carnitine deficiency
	Carnitine-palmitoyl transferase	Monitor for organ-specific toxicities
Intoxicating encephalopathy	Ureagenesis	Establish central vascular access
(±*Cerebral edema*)	Branched-chain ketoacid dehydrogenase (MSUD)	Correct hypoglycemia and hypovolemia
	Organic acid (acyl-CoA) catabolism	Identify/treat precipitating stress
		Suppress endogenous catabolism
		Clear intoxicating metabolite(s)
		Prevent large and/or rapid changes of serum osmolality
		Monitor/treat cerebral edema (e.g., osmotic agents)
		Monitor for organ-specific toxicities Consider mild systemic hypothermia
Focal neuronal necrosis	Organic acid (acyl-CoA) metabolism	Correct hypoglycemia and hypovolemia

Table 44.8 (continued)

Clinical category	Metabolic pathways	Clinical priorities
(*Metabolic stroke*)	Mitochondrial disorders	Dextrose to match or exceed EGPR
		Identify/treat precipitating stress
		Correct metabolic acidosis
		Clear toxic acyl-CoA thiosters (L-carnitine therapy)
		Monitor for organ-specific toxicities
Cardiomyopathy	Glycogenolysis	Assess cardiac structure, performance, and rhythm
(*Dilated or hypertrophic*)	(Very) long-chain fatty acid oxidation	Identify/treat heart failure
	Organic acid metabolism (esp. propionyl-CoA)	Provide disorder-specific metabolic care
	Mitochondrial disorders	
	Mitochondrial ATP/ADP exchange	

Other enzyme deficiencies within the BCAA degradation system are characterized by mitochondrial accumulation of small, nonmetabolizable, potentially cytotoxic acyl-CoA thioesters (e.g., propionyl-CoA, isovaleryl-CoA, glutaryl-CoA). Intravenous L-carnitine (see below) "detoxifies" the mitochondrial matrix to form corresponding acylcarnitines detectable by MS/MS analysis (Table 44.2). Carboxylic acid derivatives that accumulate proximal to an enzyme block are detected by gas chromatography/mass spectrometry.

Total deficiency of any one among the first four urea cyclase enzymes (CPS1, OTC, ASS1, and ASL) or the CPS1 allosteric activating system (NAGS) can result in severe hyperammonemia within days of life. Affected infants appear normal at birth but rapidly develop life-threatening cerebral edema (Fig. 44.10) accompanied by anorexia, somnolence, irregular breathing, hypothermia, dystonic posturing, seizures, and coma. In contrast, the first attack of symptomatic hyperammonemia can be delayed months or years in patients with intermediate ("partial") or distal enzyme deficiencies.

Dietary indiscretion only rarely results in clinical decompensation. More commonly, infection, dehydration, or injury triggers a mobilization and catabolism of endogenous protein that precipitates metabolic crisis.

44.6.3 General Strategies

For intoxicating IEMs, dietary indiscretion causes characteristic metabolites to increase but only rarely results in critical illness. In contrast, common infections and physiological challenges trigger a mobilization and catabolism of muscle protein that can precipitate metabolic crisis (Table 44.9). Effective treatment is predicated on establishing net protein anabolism (Fig. 44.14). Parallel and related goals are the correction and/or maintenance of critical homeostatic setpoints (e.g., blood glucose, pH, electrolytes, osmolality, etc.) and clearance of intoxicants. In practice, all of these aims are pursued simultaneously by treating the precipitating stress, delivering sufficient nutrition to shift fuel metabolism

Successful treatment of metabolic encephalopathy is predicated on controlling protein turnover, stabilizing critical homeostatic setpoints (e.g., blood glucose, osmolality, and pH), and clearing endogenous toxins from the circulation. Skeletal muscle and liver represent the major source of and sink for protein-derived toxins.

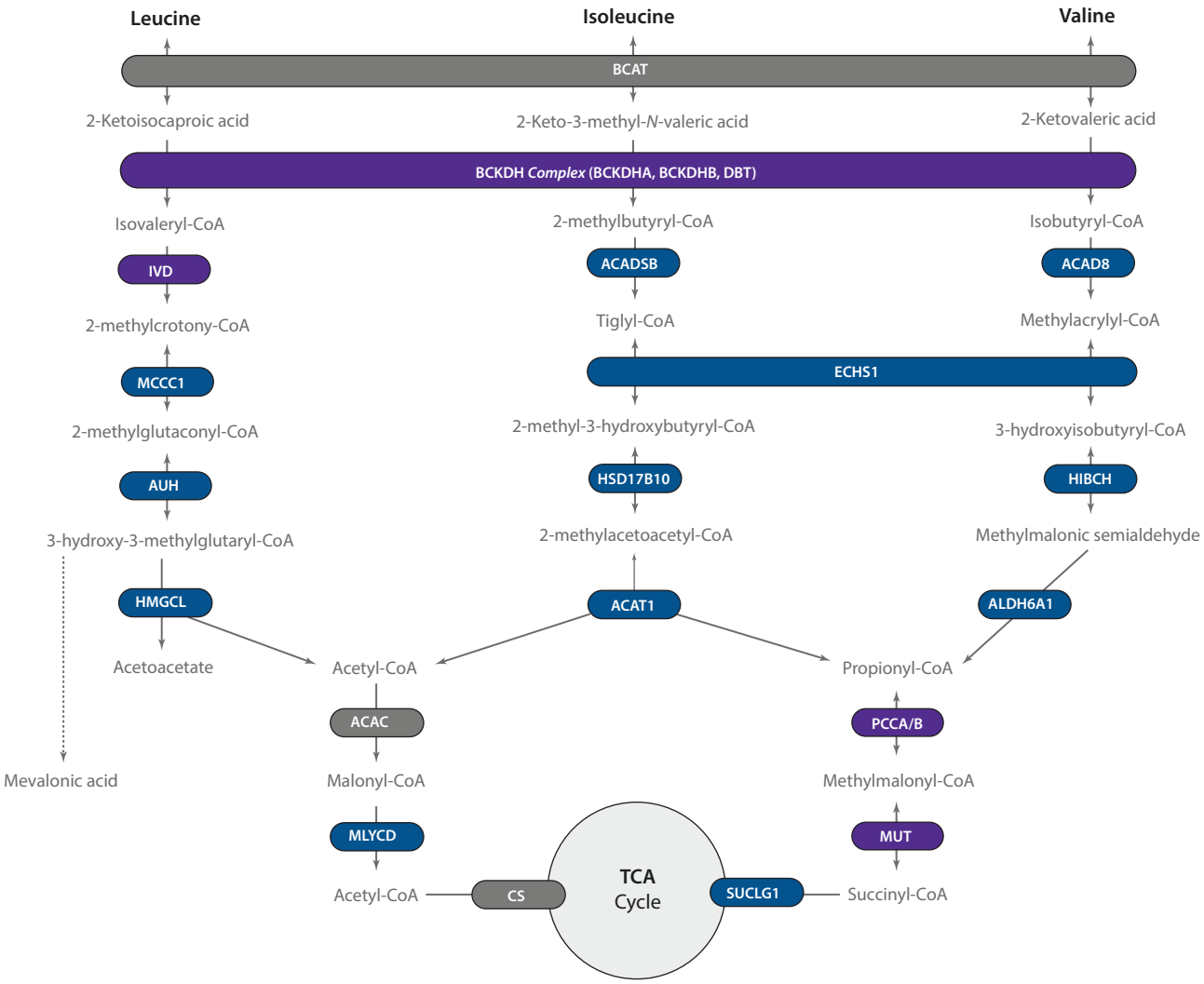

Fig. 44.12 Inborn errors of branched-chain amino acid degradation. Degradation pathways for the essential branched-chain amino acids (BCAAs; leucine, isoleucine, valine) involves two common steps – transamination (BCAT) and ketoacid oxidation (branched-chain ketoacid dehydrogenase complex [BCKDH], composed of BCKDHA, BCKDHB, and DBT subunits) – and converge on the tricarboxylic acid cycle (TCA). Biallelic mutations that disrupt BCKDH cause maple syrup urine disease. Multiple "organic acidemias" are caused by downstream enzyme defects that interfere with metabolism of branched-chain acyl-CoA thioesters in mitochondria. Enzymes are labeled using standard protein nomenclature (► http://omim.org) and shaded blue or purple (the latter are more commonly encountered) if linked to an inborn error of metabolism

Supraphysiologic calorie prescriptions used to treat metabolic crises often necessitate central venous access to prevent fluid overload, especially in older children or those with fluid-sensitive comorbidities such as cerebral edema or cardiomyopathy.

During treatment of metabolic crises, timely recognition and management of organ-specific toxicities (e.g., cerebral edema, myocardial depression, hepatopathy) critically affect outcome.

toward an anabolic state, and judiciously managing volume status, electrolyte values, and key chemical substrates (Tables 44.10 and 44.11).

For disorders of fatty acid oxidation, glycogenolysis, and gluconeogenesis, nutritional support is focused on providing sufficient glucose via dextrose infusion. MSUD and certain organic acidemias require calorie provision coupled to a customized amino acid mixture devoid of offending substrates. These mixtures can be notoriously difficult to procure and should be considered early in the course of treatment, typically in consultation with a biochemical geneticist and/or metabolic dietician. When special amino acid mixtures are not available, it is usually safe to withhold protein for 24–48 hours, but prolonged protein restriction results in selective essential amino acid deficiencies and iatrogenic complications such as anemia, hair loss, skin rashes, mucosal breakdown, and impaired immunity. In this context, special medical foods delivered

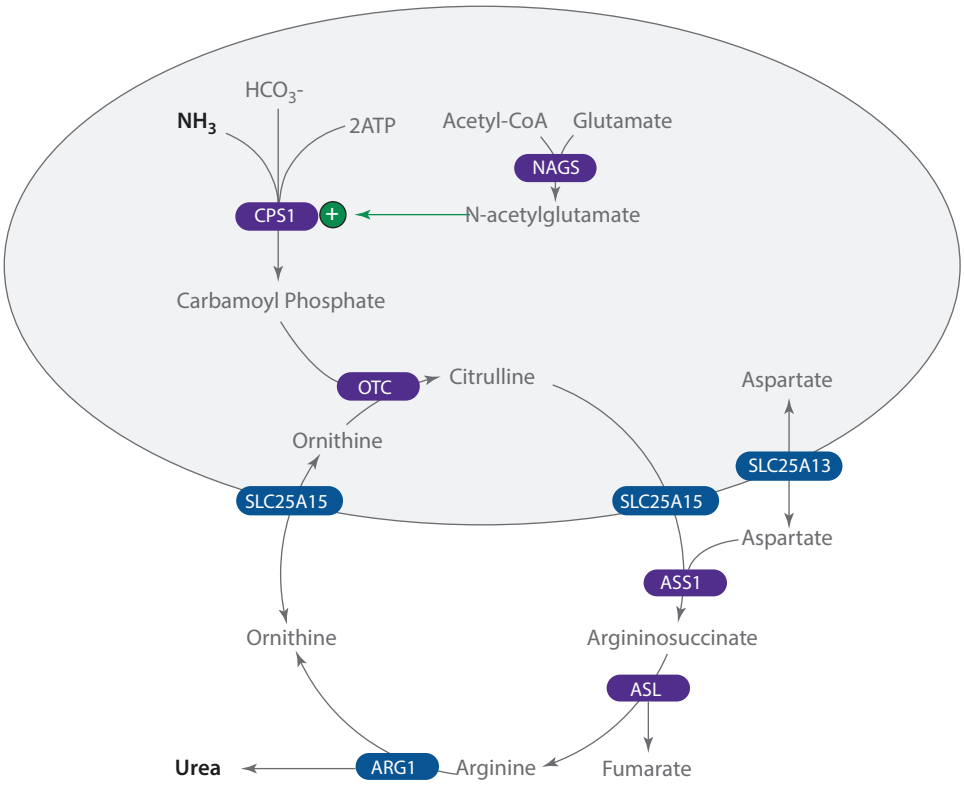

Fig. 44.13 Urea cycle disorders. Intact ureagenesis requires five enzymes (CPS1, OTC, ASS1, ASL, ARG1), two transporters (SLC25A15, SLC25A13), and an allosteric activating system (NAGS). Ureagenesis is compartmentalized between cytosol and mitochondrial matrix (gray shaded area). Severe deficiency of a proximal urea cycle enzyme (shaded purple) presents with the triad of hyperammonemia, encephalopathy, and respiratory alkalosis within a few days of life [Standard protein nomenclature (► http://omim.org)]

Table 44.9 Indications for hospitalization in children with classical maple syrup urine disease ($n = 28$)

Clinical indication	Percent
Viral gastroenteritis	39%
Viral bronchiolitis	11%
Bacterial sinusitis	11%
Neonatal (transitional) encephalopathy	11%
Urinary tract infection	7%
Cellulitis	4%
Influenza	4%
Viral meningitis	4%
Bacterial pharyngitis	4%
Esophageal candidiasis	4%
Appendicitis	4%

continuously by nasogastric tube can play a pivotal role in meeting essential amino acid requirements and reversing catabolic states.

Total nutritional goals can be met using both enteral and parenteral routes of administration. In ill neonates or children otherwise able to tolerate enteral feeding, special medical formula (0.7–1.2 kcal/mL) via nasogastric tube (30–60 mL/hour) is an effective nutritional adjunct. For older children and adults

For most IEMs that produce protein-derived toxins, protein is withheld for the first 24–48 hours of therapy, but prolonged protein restriction entails risk of essential amino acid deficiency and its associated complications.

For patients able to tolerate enteral feeding, continuous nasogastric delivery of special medical formula can substantially contribute to total nutritional goals.

The mainstay of treatment for disorders of glycogenolysis, gluconeogenesis, and fatty acid oxidation is timely infusion of dextrose to meet or exceed the EGPR.

Treatment of certain IEMs (e.g., maple syrup urine disease) requires prescribed quantities of customized amino acid mixtures which are often difficult to procure and should be considered early in the course of therapy in consultation with a metabolic specialist.

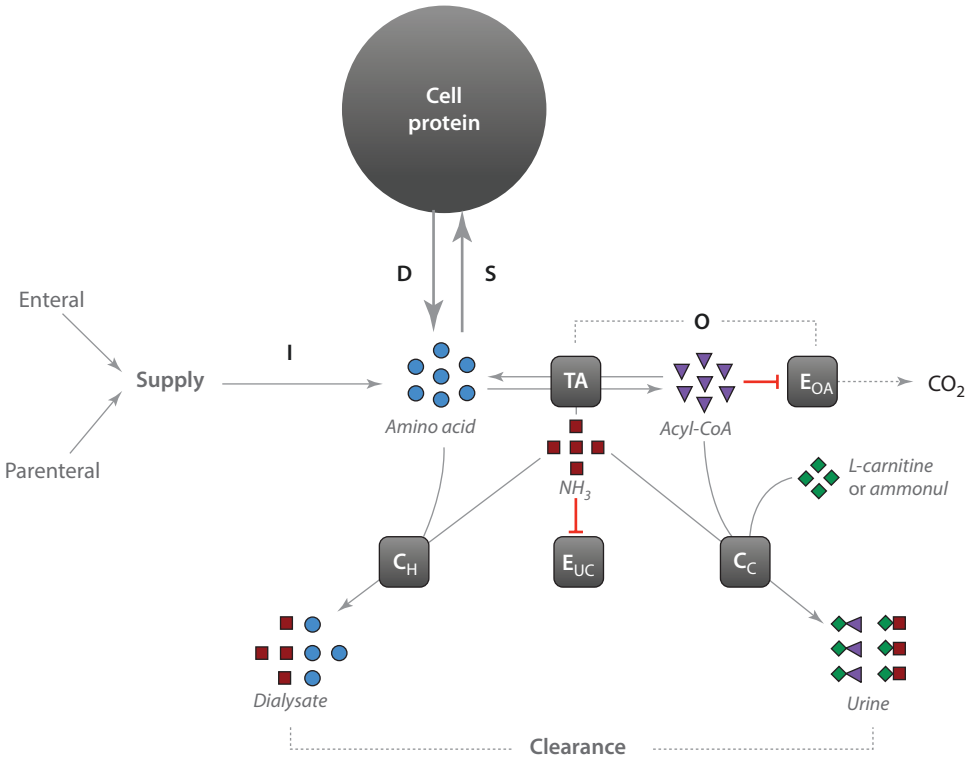

Fig. 44.14 General treatment strategies. Normally, transamination of amino acids (TA; blue circles) produces ammonia (red squares) and acyl-CoA thioesters (purple triangles) for ureagenesis (E_{UC}) and oxidation (O; E_{OA}), respectively. If either pathway is blocked, metabolites accumulate at a rate that reflects the balance among enteral and parenteral intake (I), proteolysis (D), and protein synthesis (S). When (D+I) > S, net substrate flow leads to accumulation of protein-derived toxins. Under these conditions, reversal of metabolic crisis depends on restricting intake (I) and shifting the balance of protein turnover so that S > D. Extracellular toxins are removed by hemodialysis (C_H). Intracellular toxins are cleared through conjugation (green diamonds; C_C) with compounds such as L-carnitine (for acyl-CoAs) and Ammonul (for ammonia)

Table 44.10 Maple syrup urine disease: acute management of metabolic crisis

Primary clinical goals
Decrease plasma leucine concentration by 500–1000 μmol/L per 24 hours
Prevent serum osmolality from decreasing >5 mOsm/kg H_2O per day (0.20 mOsm/kg H_2O per hour)
Maintain serum sodium concentration of 138–145 mEq/L with minimal fluctuation
Monitor and treat for signs of intracranial hypertension and impending brain herniation
Anticipate and prevent iatrogenic electrolyte abnormalities associated with high intravenous fluid, glucose, and insulin infusions (e.g., hyper- or hypoglycemia, hyponatremia, hypokalemia, hypophosphatemia)
General measures
Identify and treat precipitating catabolic stress (e.g., infection, dehydration, trauma)
Establish euvolemia using *isotonic* sodium chloride solutions
Establish central venous access
Schedule antipyretics (e.g., acetaminophen, ibuprofen, ketorolac[a]) to control fever
Administer antiemetics (e.g., ondansetron) to control nausea and vomiting
Limit use of glucocorticoids and vasoactive catecholaminergic agents

Table 44.10 (continued)

Minimize agitation and physical pain
Metabolic treatment
Provide 1.5- to 3-times EER as dextrose (50–70%) and lipid (30–50%)[b]
When central access allows, use 25% dextrose solutions to minimize complications of hypervolemia
Continuous insulin infusion: 0.02–0.15 units/kg•hour; titrate to blood glucose[c] 100–160 mg/dL
Total protein intake (enteral + parenteral)[d]: 2.0–3.5 g/kg•day as BCAA-free amino acids
Isoleucine and valine supplements (enteral + parenteral[e]): 20–120 mg/kg•day *each*; titrate to plasma concentrations of 400–800 μmol/L
Cerebral edema
Monitor for signs of intracranial hypertension and impending brain herniation
Administer hypertonic (3%) saline drip: 5–15 mEq/kg•day sodium chloride; titrate to serum osmolality 290–300 mOsm/kg, serum sodium 138–145 mEq/L, and serum osmolality *change* <0.2 mOsm/kg H_2O•hour (5 mOsm/kg H_2O•day)
Treat symptomatic hypoosmolality or worsening signs of intracranial hypertension using the following agents alone or in sequence: mannitol 0.5–1 g/kg•dose; hypertonic (3%) saline 2–3 mEq/kg•dose; furosemide 0.5–1.0 mg/kg•dose
For obtunded patients with cerebral edema, consider endotracheal intubation for airway protection and neurosurgical consultation to consider intracranial pressure monitoring, active CSF drainage, etc.
Laboratory monitoring
Serum (and/or point-of-care) glucose every 4–6 hours
Serum osmolality and electrolytes every 6–12 hours
Plasma amino acids, serum phosphorus, and magnesium every 12–24 hours
Serum lipase, amylase, and transaminases every 24–48 hours

Notes

[a]Ketorolac has potent effects on renal blood flow; it is contraindicated in patients who are dehydrated, known to have kidney disease, or taking other medications that affect renal perfusion

[b]In older children and adults, calorie intakes 3-times EER (i.e., 6000 calories per day) are sometimes necessary to drive a net shift to protein anabolism but necessitate central venous access

[c]Blood glucose can be measured from serum samples or using reliable point-of-care methods

[d]Parenteral MSUD amino acid solutions are available from only a very limited number of specialty pharmacies, and often prove difficult to procure in a timely manner. For patients of any age who can tolerate enteral feeding (even if intubated), continuous nasogastric delivery (30–60 mL/hour) of a BCAA-free MSUD formula (0.7–1.2 kcal/mL) supplemented with 1% liquid solutions of isoleucine and valine can be an effective way to meet protein goals while providing additional calories in the form of intravenous dextrose and/or lipid

[e]For parenteral administration, isoleucine and valine are each prepared as separate 1% solutions in normal saline

Table 44.11 Organic acidemias: acute stabilization of metabolic crisis

Primary clinical goals
Suppress endogenous protein catabolism
Provide adequate energy substrate as dextrose
Correct metabolic acidosis
Clear mitochondrial acyl-CoA thioesters (carnitine transesterification)
Anticipate and prevent iatrogenic glucose and electrolyte abnormalities
Monitor and treat signs of organ-specific toxicity[a]
General measures
Identify and treat precipitating catabolic stress (infection, dehydration, trauma)
Establish and maintain euvolemia using *isotonic* sodium chloride solutions
Schedule antipyretics (e.g., acetaminophen, ibuprofen, ketorolac[b]) to control fever
Administer antiemetics (e.g., ondansetron) to control nausea and vomiting
Limit use of glucocorticoids and vasoactive catecholaminergic agents
Minimize agitation and physical pain
Metabolic treatment
Stop protein intake for ≥ 24 hours[c]
Provide dextrose infusion ≥EGPR[d]
Correct base deficit with intravenous bicarbonate or acetate (1–3 mEq/kg•day)
Intravenous L-carnitine (100 mg/mL): 50–100 mg/kg•dose every 6–8 hours
Laboratory monitoring
Serum (and/or point-of-care) glucose every 4–6 hours
Serum electrolytes and venous pH every 6–12 hours

Notes

[a]e.g., Echocardiogram, electrocardiogram, and cardiac enzyme panel for patients with propionic acidemia; liver and pancreatic enzymes for select IEMs; brain MRI for any patient with signs of acute neurological regression

[b]Ketorolac is contraindicated in patients who are dehydrated, known to have kidney disease, or taking other medications that reduce renal blood flow

[c]Introduce protein or administer customized amino acids solutions in consultation with a metabolic specialist

[d]Endogenous glucose production rate (EGPR) = $6.50 \times 2.72^{-0.145 \times \text{age in years}} + 1.93$

in metabolic crisis, it is considerably more challenging to meet nutritional goals. Patients in this age group have lower basal rates of tissue accretion and often need a large calorie surplus to achieve an anabolic state. In practice, this requires central venous access to avoid complications of fluid overload.

Interventions that actively clear metabolites (e.g., hemodialysis and/or intravenous nitrogen scavengers; discussed below) are used in some clinical circumstances under the guidance of appropriate subspecialists. Finally, timely

recognition and appropriate management of comorbid complications such as cerebral edema, myocardial depression, rhabdomyolysis, pancreatitis, and liver failure critically affect outcome (Table 44.7).

44.6.4 Energy Requirements

Total energy expenditure in children is comprised of the resting energy expenditure (REE) for normal physiological functions (e.g., respiration, circulation, thermostability, and maintenance of electrochemical gradients), energy linked to physical activity, and energy invested in new tissue growth. The distribution of metabolic activity by organ shifts over the lifespan (Fig. 44.4), owing largely to differential changes in organ growth. Heart and kidney cells have the highest metabolic demand per weight of tissue but the brain has higher proportional mass. By late adolescence, muscle comes to occupy 30–40% of body mass and the majority of REE is equally distributed among brain, liver, and skeletal muscle. During metabolic decompensation and reversal, liver and skeletal muscle represent the major source and sink for toxic metabolites.

A variety of empirically derived formulas are used to calculate estimated energy requirement (EER), but the doubly labeled water method represents the most accurate standard and forms the basis for predictive equations published

The estimated energy requirement (EER) should be considered the *treatment minimum* for a child in metabolic crisis. Considerably higher energy intakes (e.g., 1.5- to 3-times EER) are often necessary to reverse catabolic states.

Actual energy expenditure in hospitalized children varies as much ±50% from EER, and this mismatch is not predicted by the type or severity of disease.

Table 44.12 Estimating energy requirements for a patient with an inborn error of metabolism

Age group	Estimated energy requirement (EER), in kcal/day =	
	Both sexes	
0–3 months	(89*w*–100) + 175	
4–6 months	(89*w*–100) + 56	
7–12 months	(89*w*–100) + 22	
13–35 months	(89*w*–100) + 20	
	Female	*Male*
3–5 years	352 + PA(11.6*w* + 347*h*)	358 + PA(16*w* + 356*h*)
6–8 years	135.5–30.8*a* + PA(10*w* + 934*h*) + 20	88.5–61.9*a* + PA(26.7*w* + 903*h*) + 20
9–18 years	135.5–30.8*a* + PA(10*w* + 934*h*) + 25	88.5–61.9*a* + PA(26.7*w* + 903*h*) + 25
Adult (≥19 years)	354–6.9*a* + PA(9.4*w* + 726*h*)	662–9.53*a* + PA(15.9*w* + 539.6*h*)

Notes and Abbreviations: For EER equations, *a* = age in years; *h* = height in meters; *w* = weight in kg. The "PA" coefficient corrects for physical activity and ranges from 1.0 (sedentary) to 1.56 (very active) in children; however, the PICU patient is typically sedentary and thus PA is assumed to be 1.0 [Taken from Otten et al. Eds. (2006), Institute of Medicine; *Suggested Readings*]

Table 44.13 Rapid bedside estimates: nutritional requirements as a function of age, sex, and body size

				EER (kcal/kg•day)[b]			Protein (g/kg•day)[c]			
Age in years	**Weight (kg)[a]**	**Length (m)[a]**	**BSA (m^2)**	**Female**	**Male**	**Indexed EER (kcal/m^2•day)**	**EAR**	**RDA**	**Indexed protein (g/m^2•day)**	**EGPR[d] (mg/kg•min)**
0	3	0.50	0.21	114	114	1650	1.52	1.52	22	8.4
1	10	0.75	0.49	81	81	1650	1.00	1.20	24	7.6
3	15	0.95	0.65	57	62	1380	0.87	1.05	24	6.1
9	30	1.33	1.10	48	52	1360	0.76	0.95	26	3.7
12	41	1.50	1.30	39	44	1320	0.76	0.95	30	3.1
18	60	1.70	1.70	30	36	1160	0.72	0.85	30	2.4

[a]Value listed is the mean for age, averaged for females and males, according to World Health Organization reference standards

[b]Estimated energy requirement (EER) is calculated using equations published by the National Academy of Sciences [Otten et al., Eds. (2006); *Suggested Readings*] based on the doubly labeled water method and assuming the patient is sedentary during hospitalization. For the patient with an unstable IEM, these should be considered *minimum* treatment goals; to promote net protein anabolism during metabolic crisis often requires energy prescriptions 1.5- to 3-times the EER

[c]Estimated average requirement (EAR) and recommended dietary allowance (RDA) represent the daily protein intake estimated to meet requirements for 50% and 98%, respectively, of healthy individuals. For IEMs, total protein is supplied as a combination of "complete" protein and a nonoffending amino acid blend specific to the metabolic defect. For several disorders (e.g., MSUD), the quantity and composition of administered amino acids are critical to optimal metabolic control and should be determined in close consultation with a biochemical geneticist and/or metabolic dietician

[d]Dextrose is typically infused as a 10% or 25% solution, depending on venous access and patient volume status. In general, exogenous glucose delivery should meet or exceed the calculated endogenous glucose production rate (EGPR). [See Huidekoper et al. (2014); *Suggested Readings*]

by the National Academy of Sciences in 2006 (▶ https://www.nap.edu/download/11537), amended for the 3- to 5-year age group in 2014 (◘ Table 44.12). Energy equations listed in ◘ Table 44.12 include a coefficient (PA) that accounts for variable physical activity, which can increase energy expenditure more than 2-fold. ◘ Table 44.13 is intended as a bedside shortcut for the busy intensivist: it lists calculated EERs and "maintenance" protein requirements adjusted for age, sex, average size, and body surface area based on the assumption that most critically ill children are sedentary (PA coefficient of 1.0).

For the purpose of treating patients in metabolic crisis, values in ◘ Table 44.13 represent *therapeutic minimums*; in dangerous catabolic states (e.g., hyperleucinemia, hyperammonemia), calorie intakes 1.5- to 3-times EER accompanied by infusions of insulin and amino acids are often necessary to establish anabolic control (◘ Table 44.10). To provide supraphysiologic energy within a safe fluid volume, total calories are often distributed between dextrose (10–25 g/dL) and intralipid (20 g/dL). For MSUD patients in crisis, we provide 50–70% of calories as dextrose and 30–50% as intralipid, but the optimal ratio is unknown. Skeletal muscle efficiently oxidizes fat during exercise and starvation; however, this pattern may not apply to a sedentary patient on simultaneous infusions of dextrose, insulin, and intralipid. Insulin-stimulated glucose oxidation normally increases cellular concentrations of malonyl-CoA, a potent inhibitor of CPT1 and long-chain fatty acid uptake into mitochondria, setting up potential competition between fuels at the cellular level.

Resting energy expenditure varies as much as 50% among healthy adults of comparable lean body mass, i.e., between 600 and 1500 kcal/m^2•day. Indirect calorimetry measurements reveal similar interindividual variation among critically ill children, with the ratio of measured versus predicted energy expenditure ranging from 0.44 to 1.53. This mismatch is not predicted by the type or severity of disease. The clinical implication of such a variation is that calories are commonly over- or underprescribed to patients in metabolic crisis. This can influence both the efficacy of therapy and its risk for complications. For example, persistent hypertriglyceridemia and hyperglycemia may reflect overfeeding in a metabolically unstable patient, whereas treatment-resistant catabolism might signal energy expenditure that exceeds the predicted value, indicating the need for more calories.

Certain forms of critical illness traditionally considered "hypermetabolic" (e.g., multisystem trauma, cancer, burns) typically do not alter REE but can have a profound effect on protein turnover (◘ Fig. 44.8). In contrast, fever from any cause has a well-established energy cost. As a general rule, metabolic heat production increases energy expenditure 10–14% per 1° centigrade (i.e., 7% per 1° Fahrenheit). This relationship is not fixed but depends on a number of variables such as body size, ambient temperature, and fever duration. Nevertheless, aggressive antipyresis is a priority for patients in metabolic crisis. Several cytokines that stimulate fever (e.g., interleukin-6, TNF-α) also drive muscle proteolysis.

Dextrose 10% at maintenance rate approximates EGPR in children ≥5 years of age, but higher rates are required for younger children. Dextrose 25% via central venous line consistently meets or exceeds EGPR at submaintenance infusion rates, minimizing complications of hypervolemia.

44.6.5 Glucose and Insulin Infusions

For any child in metabolic crisis, dextrose is infused to meet or exceed EGPR. ◘ Figure 44.15 illustrates the relationship between EGPR and commonly used infusions of 5%, 10%, and 25% dextrose. Dextrose 10% at maintenance approximates EGPR in children ≥5 years of age and nearly meets demand in younger children. In patients who require hypercaloric feeding to suppress endogenous protein catabolism, dextrose 10% at 1.5-times maintenance consistently exceeds EGPR, and dextrose 25% does so at submaintenance infusion

Insulin infusion (0.02–1.5 U/kg•hour) reduces the generation of protein-derived toxins and, when used in parallel with a supraphysiologic dextrose infusion rate, is titrated to blood glucose concentrations of 100–160 mg/dL.

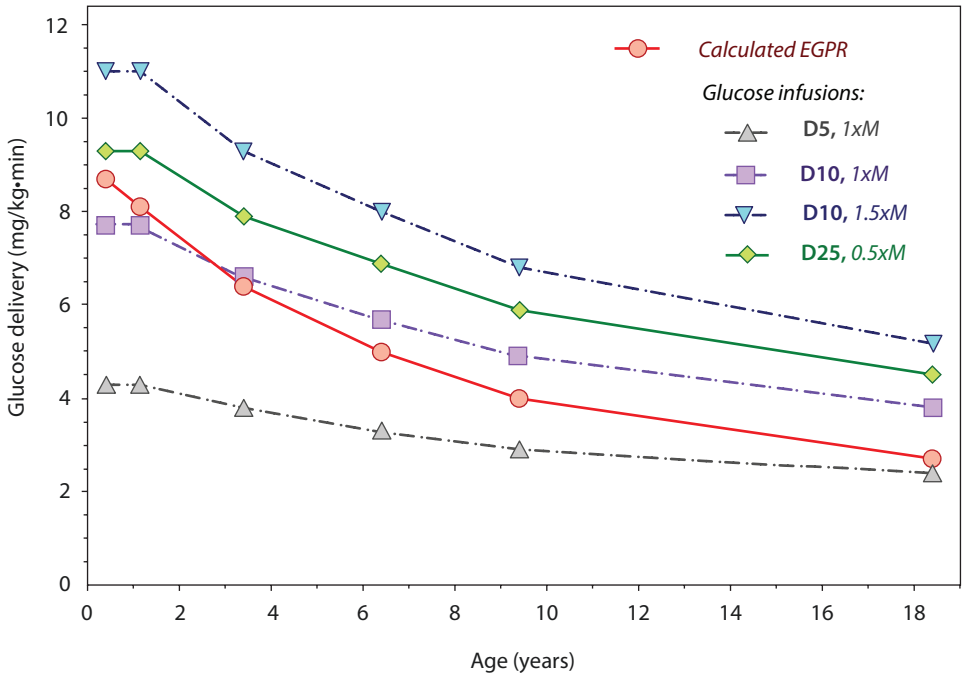

Fig. 44.15 Glucose infusions and endogenous glucose production rate. Red circles depict the age-dependent endogenous glucose production (EGPR) from combined actions of glycogenolysis and gluconeogenesis, where EGPR = $6.50 \times 2.72^{-0.145 \times \text{age in years}} + 1.93$, expressed in mg/kg•min. For a child in metabolic crisis, dextrose infusion should match or exceed EGPR. Dextrose 10% at maintenance (purple squares) approximates EGPR in children ≥5 years of age, and at 1.5-times the maintenance rate (blue triangles) consistently exceeds EGPR. Dextrose 25% via central line (green diamonds) exceeds EGPR at 50% maintenance rate, minimizing complications of hypervolemia in patients with cerebral edema, congestive heart failure, or renal insufficiency. Dextrose 5% solutions (gray triangles) are not appropriate for treatment of metabolic crises. (Data recalculated and rendered after Huidekoper et al. (2014), *Suggested Readings*)

rates, minimizing iatrogenic complications of hypervolemia in children with cerebral edema, cardiomyopathy, or renal insufficiency.

Insulin acts through a transmembrane tyrosine kinase receptor (INSR) to antagonize the actions of several counterregulatory hormones and is thus a powerful ally in the reversal of catabolic states. Activation of INSR in muscle increases glucose uptake, glycolysis, and glycogen synthesis while suppressing glycogen breakdown. In adipocytes, insulin inhibits lipolysis and stimulates triacylglycerol storage. Insulin is primarily used for its effects on protein turnover; in both liver and muscle, INSR activation increases tissue uptake of amino acids and exerts both anabolic (synthetic) and anti-catabolic actions, shifting overall protein balance toward net accretion.

Insulin is generally contraindicated for treatment of glycogen storage and fatty acid oxidation disorders, but its anabolic effects are especially useful for reducing the generation of protein-derived toxins such as leucine and ammonia. In patients with MSUD and UCDs, we thus recommend continuous insulin (e.g., 0.02–0.15 units/kg•hour) to parallel supraphysiologic dextrose infusions, titrated to blood glucose concentrations of 100–160 mg/dL (Table 44.10).

Intravenous L-carnitine (100 mg/mL) clears cytotoxic acyl-CoA thioesters from the mitochondrial matrix and increases cellular availability of unconjugated CoA. Short-chain acylcarnitine formation appears to saturate at doses of 200–400 mg/kg•day.

44.6.6 L-Carnitine Therapy

Three acyltransferases catalyze transesterification of short-carbon chains between acyl-CoA thioesters and L-carnitine (Fig. 44.16); they primarily localize to mitochondria and their action is reversible. High mitochondrial concentrations of L-carnitine and an acyl-CoA thioester (e.g., propionyl-CoA) drive formation of the corresponding acylcarnitine (e.g., propionylcarnitine).

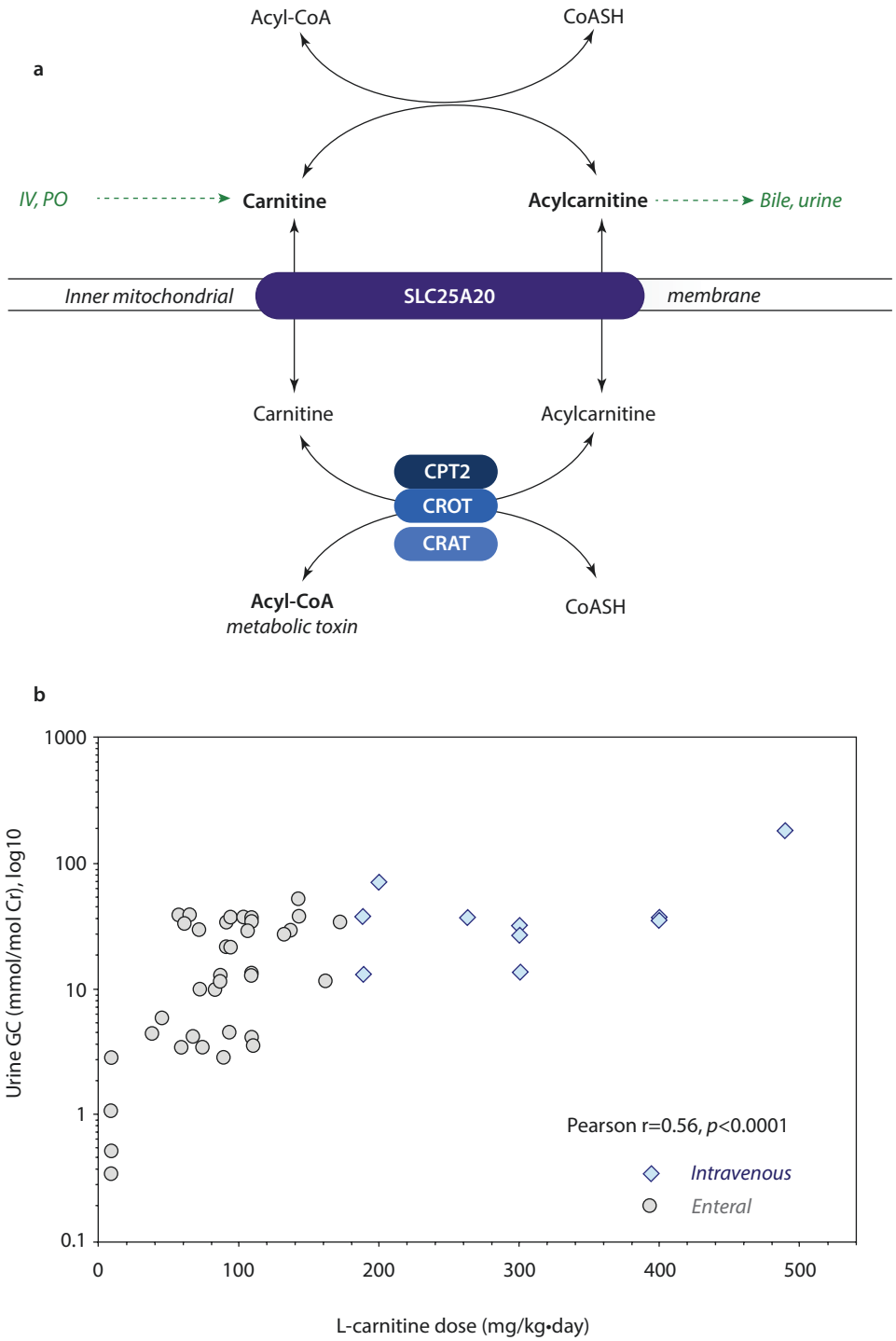

Fig. 44.16 Intravenous L-carnitine therapy. (**a**) Three reversible acyltransferases (CRAT, CROT, CPT2; ▶ http://omim.org) with overlapping chain length specificity catalyze transesterification of carbon chains between acyl-CoA thioesters and L-carnitine in mitochondria. High intracellular concentrations of L-carnitine and an acyl-CoA drive formation of the corresponding acylcarnitine and increase availability of unconjugated CoA (CoASH). Heteroexchange of L-carnitine and acylcarnitines across the inner mitochondrial membrane is mediated by a translocase (SLC25A20), and acylcarnitine derivatives are excreted in urine and bile. (**b**) Among children with glutaric acidemia type 1, enteral L-carnitine doses >100 mg/kg•day (gray circles) are associated with gastrointestinal side effects. Formation of glutarylcarnitine (GC), the product of glutaryl-CoA and L-carnitine conjugation, appears to saturate at intravenous L-carnitine doses of 200–400 mg/kg•day (blue diamonds)

Specific carnitine acyltransferases differ with regard to chain length specificity but show some overlap in substrate utilization.

Carnitine acetyltransferase (CRAT) is the most abundant enzyme in the class, utilizes substrates with 2–10 carbons, and has high activity toward short-chain compounds (e.g., acetyl- and propionyl-CoA). It is the principle catalyst for acyl-CoA thioesters of amino acid degradation (Fig. 44.12), which typically contain ≤6 carbons. Medium- (CROT; 6–12 carbons) and long-chain (CPT1 and CPT2; 12–22 carbons) acyltransferases play a more important role in transesterification of fatty acid oxidation intermediates.

Intravenous L-carnitine is used to treat a variety of IEMs with the goal to clear toxic acyl-CoA thioesters from the mitochondrial matrix and increase the availability of unconjugated CoA (Fig. 44.16). Many hospitals stock L-carnitine for intravenous injection (100 mg/mL) and its administration to children in metabolic crisis is widely practiced. High intravenous doses of L-carnitine appear safe but, with the exception of systemic primary carnitine deficiency (SLC22A5; OMIM 212140), are not proven to hasten recovery from metabolic illness or improve outcome.

Quantitative aspects of L-carnitine dosing are poorly understood. Enteral doses >100 mg/kg•day are associated with gastrointestinal symptoms and a "fishy" odor. Studies in hospitalized patients suggest that CRAT-mediated formation of short-chain acylcarnitine conjugates may saturate at intravenous L-carnitine doses of 200–400 mg/kg•day (Fig. 44.16). For patients with organic acidemias in metabolic crisis, we administer 50–100 mg/kg•dose every 6–8 hours (Table 44.11). The metabolic response to this therapy can be quantified by urinary excretion of acylcarnitine conjugates.

44.6.7 Ammonia Removal

The neurotoxicity of ammonia is related to its pH-sensitive biodistribution across the blood-brain barrier and the rate of glutamine synthesis from glutamate and NH_3 in cerebral astrocytes.

Infants and children with proximal urea cycle defects often present comatose with ammonia levels of 500–4000 μmol/L. Hemodialysis is the most efficient method of ammonia removal when blood ammonia is increasing rapidly, resistant to nitrogen scavenger therapy, and/or persistently ≥350 μmol/L.

44.6.7.1 General Considerations

Urea cycle disorders (Fig. 44.13) are characterized by a triad of hyperammonemia, encephalopathy, and respiratory alkalosis. Ammonia can increase to dangerous levels in certain organic acid disorders (e.g., PPA, MMA) but coincides with metabolic acidosis that may afford some protection against hyperammonemic encephalopathy. The blood ammonia concentration at which individuals become symptomatic is related, among other factors, to its pH-sensitive biodistribution across the blood-brain barrier and conversion to glutamine in cerebral astrocytes (Fig. 44.11). Most patients become symptomatic at blood ammonia concentrations >200 μmol/L and, notwithstanding some clinical variation, hyperammonemic encephalopathy follows a progression:

- Ammonia 200–400 μmol/L: Conscious but drowsy, progressing to obtundation
- Ammonia 400–600 μmol/L: Unconscious but responsive to pain with purposeful movement (e.g., flexion/withdrawal); with deepening encephalopathy, extensor response to pain
- Ammonia >600 μmol/L: Deep coma; unresponsive to pain

During acute crises, patients with UCDs often have ammonia levels of 500–4000 μmol/L and are profoundly compromised. In this context, low plasma citrulline, high plasma glutamine (>800 μmol/L), and high urine orotic acid (>20 μmol/mmol creatinine) indicate a proximal UCD (e.g., NAGS, CPSI or OTC; Fig. 44.13).

While implementing nutritional therapy to control protein turnover (Fig. 44.7), excess ammonia can be removed from the circulation by hemo-

dialysis and/or medications (Fig. 44.14). Hemodialysis is the quickest and most efficient method of nitrogen removal and should be promptly implemented if blood ammonia is increasing rapidly, resistant to scavenger therapy, and/or persistently ≥350 μmol/L. Historically, hemodialysis has been employed for ~60% of neonatal hyperammonemic crises and ~10% of crises in older children.

Animal studies and a few case reports indicate that mild systemic hypothermia might suppress ammonia production and provide some degree of protection against hyperammonemic encephalopathy. However, this strategy introduces additional risks and the data in support of it are at present inconclusive.

44.6.7.2 Pharmacology

- *Intravenous nitrogen scavengers*: Phenylacetate condenses with glutamine to form phenylacetylglutamine (two nitrogen atoms) and benzoate combines with glycine to form hippurate (one nitrogen atom); both are excreted in urine (Figs. 44.11 and 44.14). A parenteral combination of sodium phenylacetate and sodium benzoate (Ammonul™; 100 mg/mL each) was approved by the FDA in 2005 and increases survival from hyperammonemic encephalopathy (73% versus 16% among infants ≤30 days of age; 98% versus 72% among older patients). Ammonul is compatible with hemodialysis and can be mixed directly with injectable arginine hydrochloride (10%) to treat patients with CPS1, OTC, ASS1, or ASL deficiency (Table 44.14). It is diluted with dextrose 10% before administration and infused via central line as loading (60–120 min) followed by maintenance (24 hours) doses. Adverse effects occur in half of patients and include electrolyte disturbances, seizures, and respiratory distress.
- *Arginine*: With the exception of arginase deficiency (ARG1; OMIM 207800), UCDs prevent formation of arginine and render this amino acid

Intravenous sodium phenylacetate/sodium benzoate (Ammonul™, 100 mg/mL each) is an FDA-approved therapy that provides alternate routes of nitrogen excretion and improves survival from hyperammonemic crises.

With the exception of arginase deficiency, UCDs prevent the formation of arginine and render this amino acid "conditionally essential."

Carglumic acid is reserved for the treatment of N-acetylglutamate synthetase deficiency.

To reduce the risk of prescribing errors, hospitals that manage children with acute hyperammonemia can incorporate standardized order sets for intravenous Ammonul and arginine hydrochloride therapy into the electronic health record.

Table 44.14 Intravenous pharmacological therapy for acute hyperammonemia

Weight and disorder	Infusion components		Dose provided[b]		
	Ammonul[a]	Arginine HCl (10%)	Sodium phenylacetate	Sodium benzoate	Arginine HCl
≤20 kg					
CPS, OTC[c]	2.5 mL/kg	2.0 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
ASS1, ASL	2.5 mL/kg	6.0 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
>20 kg					
CPS, OTC	55 mL/m^2	2.0 mL/kg	5.5 g/m^2	5.5 g/m^2	200 mg/kg
ASS1, ASL	55 mL/m^2	6.0 mL/kg	5.5 g/m^2	5.5 g/m^2	600 mg/kg

[a]Ammonul contains 100 mg/mL each of sodium phenylacetate and sodium benzoate
[b]Values listed represent both the loading and maintenance doses. The loading dose is diluted in a volume of 25–35 mL/kg 10% dextrose, infused over 60–120 min, and can be repeated. Maintenance infusion is prepared in the same volume (25–35 mL/kg) and infused over 24 hours, accompanied by 1- to 1.5-times maintenance fluid as dextrose 10%
[c]*Abbreviations: ASL* argininosuccinate lyase, *ASS1* argininosuccinate synthase, *CPS1* carbamyl phosphate synthase I, *OTC* ornithine transcarbamylase

"conditionally essential" (Fig. 44.13). Intravenous arginine hydrochloride (10%) is dosed in parallel with dialysis and commonly combined in solution with Ammonul. Weight-based arginine doses are 3-fold higher for ASS1 and ASL as compared to CPS1 and OTC deficiencies (Table 44.14). Intravenous arginine is a substrate for nitric oxide formation and, therefore, can lower blood pressure.

- *Citrulline and carglumic acid*: Enteral citrulline is provided for enzyme defects proximal to ASS1 (e.g., NAGS, CPS1, and OTC) based on a theoretical advantage of incorporating aspartate nitrogen into urea for clearance. The weight-based enteral daily dose is 200 mg/kg (≤20 kg) or 4 g/m^2 (>20 kg) divided in multiple increments. Carglumic acid is FDA-approved for the treatment of hyperammonemia associated with NAGS (OMIM 237310); during acute crises, 100–250 mg/kg•day is administered in 2–4 daily doses.

Pharmacological therapy for acute hyperammonemia is relatively complex and required infrequently; it is therefore subject to prescribing errors. To reduce the risk of such errors, it is prudent for hospital pharmacies that dispense Ammonul and arginine to incorporate standard order sets for these agents into the electronic health record.

44.7 Hemodialysis

For children in MSUD crisis, nutritional therapy alone can reduce extreme elevations of leucine and α-ketoisocaproic acid but short courses of hemodialysis accelerate the clearance of toxic metabolites. Simultaneous control over protein turnover is necessary to prevent rebound intoxication.

In patients with MSUD, nutritional therapy alone can reduce extreme elevations of leucine and α-ketoisocaproic acid but hemodialysis accelerates the clearance of BCAAs. To prevent recurrent intoxication, hemodialysis must be coupled with therapies that reduce protein catabolism. A combined approach can be highly effective (Fig. 44.17). Venovenous hemofiltration and peritoneal dialysis are less favorable and more dangerous methods of leucine removal.

Invasive ammonia removal is optimized with continuous arteriovenous or venovenous hemodialysis at flow rates of 150 mL/m^2•min and can be combined with extracorporeal membrane oxygenation (flow rates 170–200 mL/m^2•min) to achieve even faster detoxification.

Infants with severe hyperammonemia (≥350 μmol/L) should be promptly hemodialyzed using a target blood flow of 150 mL/m^2•min through the largest catheter consistent with body size. The rate of ammonia clearance (mL/min) approximates flow rate (mL/min) through the dialyzer. Hemodialysis clears ammonia ~10-times faster than peritoneal dialysis or hemofiltration. Exchange transfusion is ineffective.

Extracorporeal membrane oxygenation (ECMO) with hemodialysis provides high flow rates (170–200 mL/m^2•min) but is more difficult to implement and entails higher morbidity. Hemodialysis and ECMO have limited efficacy at ammonia concentrations <200 μmol/L. Hyperammonemic rebound, resulting from both ammonia redistribution and ongoing protein catabolism, is common following a detoxification cycle.

Children receiving hemodialysis for metabolic crisis almost invariably have cerebral edema, and dialysis parameters should be carefully designed to prevent any hypotonic changes of serum osmolality that exacerbate brain swelling.

The intensivist can assume that any patient treated with hemodialysis for metabolic intoxication has concomitant cerebral edema. Therefore, dialysis parameters should be carefully designed and monitored to minimize changes of serum osmolality; a modest (i.e., 3–5%) decrease of osmolality in an obtunded MSUD patient can precipitate catastrophic cerebral herniation, even as pathological metabolites normalize.

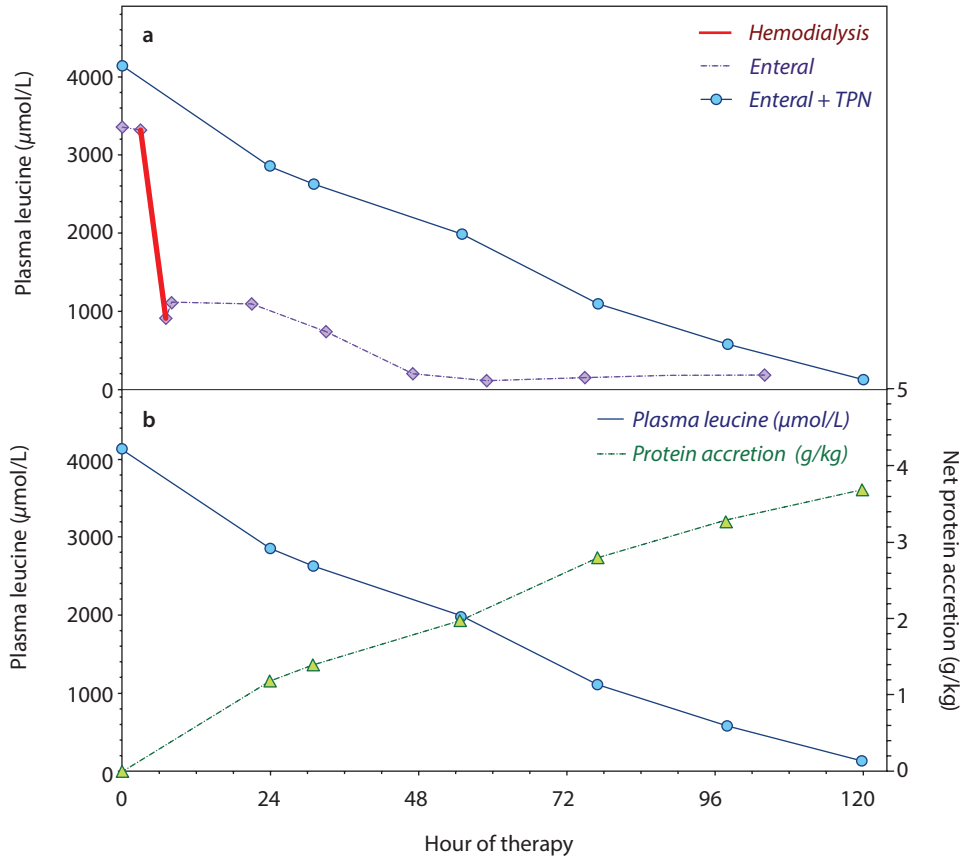

Fig. 44.17 Treatment strategies for maple syrup urine disease. (**a**) Two neonates with classical MSUD presented with metabolic encephalopathy and cerebral edema. One was managed with combined enteral and parenteral nutritional therapy (blue circles) as plasma leucine decreased from 4812 to 63 µmol/L over 120 hours. The other (purple diamonds) was treated with a combination of continuous nasogastric medical formula and a single hemodialysis run (blood flow 30 mL/min, dialysate flow 500 mL/min), which decreased plasma leucine from 3217 to 814 µmol/L over 165 min (red line). Both children recovered fully. (**b**) In an MSUD patient treated with nutritional therapy alone, the decrease of extracellular leucine concentration reflects its incorporation into protein, allowing for accurate estimation of total protein accretion (green triangles; g/kg)

44.8 Summary

Inborn errors of metabolism comprise a diverse and complex collection of monogenic disorders that commonly present with medical complications during infancy and early childhood. The intensivist working at a pediatric referral center is likely to encounter a few critically ill children with IEMs during the course of a career. Therefore, timely recognition and triage is essential and can be guided by a survey of key historical facts, exam findings, laboratory results, and imaging studies. The most dangerous IEMs either impair fasting adaptation or result in generation of protein-derived toxins. Effective treatment, therefore, depends on understanding the biological stress response, its effects on metabolic adaptation, and the manipulation of clinical variables that control glucose homeostasis and protein turnover. Comorbidities such as cerebral edema, acute liver failure, coagulopathy, cardiomyopathy, and rhabdomyolysis

often accompany metabolic crises, and their timely recognition and management are major determinants of clinical outcome.

44.9 Online Point-of-Care Resources

- *Online Mendelian Inheritance in Man (OMIM)*; ► https://www.omim.org/: OMIM is an authoritative catalog of human genes, traits, and genetic disorders. Dr. Victor A. McKusick created the database in the early 1960s as Mendelian Inheritance in Man (MIM), published in 12 editions between 1966 and 1998. The online version emerged in 1987 as a collaboration between the National Library of Medicine and the William H. Welch Medical Library at Johns Hopkins University and was made available for the World Wide Web by the National Center for Biotechnology Information (NCBI). It is currently authored and edited at the McKusick–Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine. OMIM is freely available and updated daily. It contains information about ~15,000 human genes and all known Mendelian disorders, focusing on the relationship between phenotype and genotype. Entries most useful to the clinician are coded with "#", tagged with a unique 6-digit OMIM identifier, and sometimes grouped into related categories ('phenotypic series') indicated by the letters "PS" preceding the 6-digit code. OMIM numbers are referenced within this chapter and often appear in the primary literature; they can be used to quickly locate information about a specific genetic condition.
- *GeneReviews*; ► https://www.ncbi.nlm.nih.gov/books/NBK1116/: GeneReviews is a free, online, point-of-care resource for busy clinicians treating patients with genetic disorders. It provides medically actionable information in a standardized format that emphasizes diagnosis, management, and genetic counseling. Each GeneReviews chapter is written by one or more experts in the field and undergoes rigorous editing and peer review before publication online. GeneReviews chapters are indexed on PubMed (► https://www.ncbi.nlm.nih.gov/pubmed/) and are updated every 2–4 years using a comprehensive editorial process.
- *The National Organization for Rare Disorders (NORD)*; ► https://rarediseases.org: NORD is a nonprofit patient advocacy organization dedicated to individuals with rare disorders and their clinical providers. The website provides information about identification and treatment of many genetic disorders and links to education, advocacy, research, and patient services. Within the NORD website are "Online Physician Guides" intended to help clinicians quickly recognize, diagnose, and treat specific disorders.
- *Genetics Home Reference*; ► https://ghr.nlm.nih.gov: Genetics Home Reference is a consumer health website from the National Library of Medicine (National Institutes of Health). It provides information intended for the general public but is written by professionals in genetics and public health and reviewed by experts in research and patient care. It contains clinically useful point-of-care information about many commonly encountered IEMs. The content is updated regularly.

Review Questions

(1) A healthy 3-year-old girl fasts overnight in anticipation of an early-morning tonsillectomy procedure. The surgery is unexpectedly delayed the following day, and at noon she becomes pale, agitated, and diaphoretic. Within 15 min,

she is obtunded and has a generalized tonic-clonic seizure. Her clinical presentation most likely reflects an inherited disorder of:
a) Glycosylation
b) Insulin regulation
c) Fatty acid oxidation
d) Ureagenesis
e) Cerebral glucose uptake

(2) Which of the following is *not* an important physiological action of insulin?
a) Glucose uptake and oxidation by muscle
b) Suppression of glycogenolysis in liver and muscle
c) Increased hepatic ureagenesis
d) Inhibition of long-chain fatty acid uptake by muscle and liver mitochondria
e) Suppression of muscle protein catabolism

(3) An 8-day-old infant presents to the emergency department with lethargy, dehydration, and tachypnea. Initial laboratory studies reveal serum glucose of 37 mg/dL, arterial pH of 7.1, pCO_2 of 27 mmHg, serum bicarbonate of 4 mmol/L, and an anion gap of 20 mmol/L. You call the newborn screening laboratory, who informs you that C3 acylcarnitine was modestly elevated on the newborn filter paper blood spot. The most likely cause of the anion gap is:
a) Hyperammonemia
b) Leucinosis
c) Respiratory alkalosis
d) Bacteremia
e) Hyperketosis

(4) A 15-year-old boy with propionic acidemia presents to the emergency room with lassitude, confusion, tachycardia, and Kussmaul breathing. Examination reveals a third heart sound, pitting edema in the lower extremities, jugular vein distention, and diffuse inspiratory crackles at the lung bases. Plasma ammonia (270 μmol/L) and β-hydoxybutyrate (3.2 mmol/L) are elevated. To reverse metabolic crisis, an appropriate fluid regimen is:
a) Dextrose 2.5% at 2-times maintenance
b) Dextrose 25% at 0.5-times maintenance
c) Dextrose 10% at 1.5-times maintenance
d) Dextrose 25% at 1.5-times maintenance
e) Hypertonic (3%) saline at 10 mEq/kg•day

(5) An infant with classical maple syrup urine disease presents to the hospital at 14 days of age with acute metabolic encephalopathy in the setting of viral gastroenteritis. Her calculated estimated energy requirement (EER) is 330 kcal/day. An appropriate calorie prescription to initiate therapy is:
a) 1240 kcal/day
b) 330 kcal/day
c) 660 kcal/day
d) 1000 kcal/m^2•day
e) 100 kcal/kg•day

(6) A 4-year-old boy with X-linked ornithine transcarbamylase deficiency presented to the hospital in coma with markedly elevated plasma ammonia (2400 μmol/L) and glutamine (1400 μmol/L). He is being treated with dialysis (blood flow 150 mL/m^2•min), Ammonul, and arginine hydrochloride. The

ammonia concentration has decreased to 325 μmol/L. He suddenly develops extensor posturing, bradycardia, and fixed pupillary asymmetry. Which laboratory trend is most likely to explain this abrupt change in his clinical status?

a) A rapid decrease of plasma ammonia concentration from 2400 to 325 μmol/L
b) A decrease of serum sodium concentration from 138 to 131 mEq/L
c) A decrease of blood glucose concentration from 170 to 80 mg/dL
d) Acute hyperchloremic acidosis
e) An increase of plasma glutamine concentration from 1400 to 1650 μmol/L

Answers to Review Questions

(1) C
(2) C
(3) E
(4) B
(5) C
(6) B

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Suggested Readings

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Special Topics and Populations

Contents

Trauma/Burn

Brett W. Engbrecht and Robert E. Cilley

Contents

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Learning Objectives

- Understand the Advanced Trauma Life Support (ATLS) approach to evaluation and initial treatment of the injured child.
- Understand the role of the Pediatric Critical Care specialist during the initial evaluation and ongoing care of the injured child.
- Understand ways to reduce radiation exposure to the injured child.
- Know the current treatments and risks of common thoracic, abdominal, and orthopedic injuries in children.
- Understand the implications of physical child abuse in the evaluation and treatment of injured children.
- Be able to initiate treatment of a child with a burn injury.

45.1 Overview of Pediatric Trauma Systems

Optimal care of the injured child requires a coordinated, multidisciplinary team.

A trauma system includes all participants involved in the care of injured patients in a region. In addition to the trauma center, this includes emergency medical services, regional hospitals without trauma expertise, inpatient and outpatient rehabilitation services, and injury prevention programs. At the center of the trauma system is a trauma center, a hospital that has committed resources and specially-trained personnel to care for injured patients. A trauma system for children involves regional adult trauma centers that refer the most severely injured children to the pediatric trauma center. Requirements to obtain accreditation as a trauma center vary by state. Most trauma centers in the United States are verified by the American College of Surgeons, a program that was developed in 1987, and are required to meet specific standards that vary based on the level of trauma center. Some states have their own specific accreditation process for trauma centers.

The leaders of the pediatric trauma program should have a role in the development/maintenance of the regional trauma system to ensure that the interests of injured children are prioritized. Optimal care occurs in such as system, where all components of the system function in a coordinated fashion such that the injured child receives the appropriate care at the appropriate level of trauma center in a timely manner (▶ Box 45.1).

Pediatric trauma centers require a Pediatric ICU that is managed by Pediatric Critical Care Medicine specialists. Collaboration between Pediatric Trauma Teams and Pediatric Critical Care Medicine Teams is essential in providing optimal care for severely injured children.

Box 45.1 Contributors to the Multidisciplinary Care of the Injured Child

- Pre-hospital: EMS, air and ground transport
- Emergency Medicine/Emergency Department (includes local, community referring hospitals and trauma center)
- Pediatric Trauma team (pediatric surgeons, advance practice nurses, physician assistants, case managers)
- Pediatric Critical Care Medicine/Pediatric Intensive Care Unit
- Neurosurgery/Orthopedic Surgery
- Otolaryngology/Plastic Surgery/Ophthalmology/Urology/Cardiac Surgery
- Anesthesiology
- Radiology
- Nursing (Emergency Department, Operating Room, PICU, step-down unit, floor unit)

- Social Work/Child Life/Chaplain
- Rehabilitation services (Physical/Occupational/Speech Therapy; rehabilitation medicine, concussion specialist)
- Dietician/Nutrition Support
- Clinical Support Services (laboratory services, blood bank)
- Administrative Support Services (abstractors, coders, hospital administration)
- Performance Improvement Program
- Injury Prevention Program

45.2 Demographics of Childhood Injury

The majority of childhood injuries are blunt, with penetrating injuries (gunshot, stab) accounting for fewer than 10% of patients in most series. The most common trauma mechanisms in the country are falls and motor vehicle collisions. The frequency and type of injuries seen by a pediatric trauma center are dependent upon the location of the trauma center (urban vs. rural) and the definition of "pediatric" for the individual center (most centers have an upper age limit between 14 and 21 years old). Injury prevention strategies for each center should reflect the most frequent types of injuries seen at that center.

45.3 Initial Evaluation of the Traumatically Injured Child-Role of PCCM

Most injured patients are initially evaluated at the scene of the injury by emergency medical services personnel. In addition to quickly evaluating the patient and treating life-threatening issues (e.g., airway compromise, tension pneumothorax), EMS providers determine the mode of transport and destination. The receiving facility, either a local non-trauma hospital, an accredited adult trauma center, or an accredited pediatric trauma center, is chosen based on predetermined criteria such as the mechanism of injury, types of injuries identified, hemodynamic status, and distance to local hospitals vs. regional trauma centers. Weather may also play a role, as air transport might not be available in certain weather conditions. Hospitals without trauma accreditation and adult trauma centers should have established criteria for transferring to a pediatric trauma center, and transfer agreements between these facilities should be prearranged to expedite the transfer process.

ATLS provides a systematic approach that prioritizes the diagnosis and simultaneous treatment of life-threatening injuries.

Modern trauma centers have a team of physicians, nurses, and other health care professionals that respond to trauma activations to assess and care for the injured child, with each member of the team having an assigned role. The trauma surgeon must coordinate the response of the team, maintaining priorities in evaluation and treatment based on the injuries identified. The Advanced Trauma Life Support (ATLS) approach is used. For seriously injured children, the early involvement of a PCCM physician is imperative. In some pediatric trauma centers, the PCCM physician is responsible for establishing and maintaining the airway for children, a critical, and challenging, aspect of high-quality care. The skills and expertise of PCCM physicians in vascular access, ventilator management, and management of resuscitative medications, in addition to airway management, are particularly helpful. Early involvement of the PCCM team also allows for prompt and seamless transition to the PICU for appropriate patients.

ATLS endorses a standardized approach to the evaluation of any injured patient. The "primary survey" focuses on, in order, *A*irway, *B*reathing, and *C*irculation. Critical injuries are treated as the evaluation proceeds. *D*isability (neurologic assessment) and *E*xposure/*E*nvironmental Control (completely undress patient to avoid missed injuries while also preventing hypothermia) complete the primary survey. It is of utmost importance that the primary survey is led by the trauma surgeon and proceeds in a rapid but highly organized manner. The primary survey allows the child to be assessed quickly and have treatment priorities made based on injuries that pose the greatest threat to life. The person performing the primary survey can assess the ABCDEs often in less than 1 min. Asking an older child their name and what happened allows assessment of airway patency, breathing, and cognition. A smaller child who can be consoled while crying is also reassuring. Developmental and anatomic caveats important to consider during the primary survey of a small child are summarized in ◘ Table 45.1.

The "secondary survey," which includes a complete head-to-toe assessment and reassessment of vital signs, begins when the primary survey is completed. Adjuncts to the physical exam include radiographs, CT scans, and ultrasound (FAST exam). Injuries may be stabilized or treated definitively (e.g., traction to stabilize a femur fracture vs. placement of an intramedullary nail). The trauma surgeon works with the specialists to determine which injuries to treat, the

◘ Table 45.1 Important developmental and anatomic considerations during the pediatric primary survey

Airway	Larynx and vocal cords are more cephalad Prominent tongue in small infants predisposes obstruction Trachea is short, only 5 cm in infants and 7 cm in toddlers. ETT migrates easily. Three times the ETT size often approximates tip placement (in cm) from the gums to 1 cm above the carina Infants have a prominent occiput often causing neck flexion and possible obstruction when supine. Placement of an appropriately sized cervical collar can maintain the airway in a neutral position while stabilizing the cervical spine
Breathing	Increased metabolic rate in infants necessitates respiratory rates of 30–40 bpm. In older children ventilation is maintained at rates of 16–24 bpm Respiratory acidosis must be corrected with appropriate ventilation. Sodium bicarbonate is *not* an appropriate treatment of respiratory acidosis
Circulation	Mean systolic blood pressure is 90 mm Hg + (2 × age in years) Lower limit of systolic blood pressure is 70 mm Hg + (2 × age in years) A child's increased physiologic reserves preserves systolic blood pressure even with the loss of 30% blood volume
Disability	Utilize a modified Glasgow Coma Scale (GCS) for the neurologic assessment of the infant and child The anterior fontanel remains open until 12–24 months, whereas the posterior fontanel closes by 2–4 months Open fontanels are not fully protective from the effects of increases in intracranial pressure Subarachnoid space is small and offers less protection from rotational injuries
Exposure	Infants have a limited or absent ability to shiver High ratio of body surface to body mass in children (especially infants) predisposes children to heat loss Avoidance of unnecessary heat loss is essential in children

order of treatment, and the timing of treatment. These decisions are made once the patient has been fully assessed and depend upon the types of injuries, the severity of injuries, and the hemodynamic status of the patient. Disposition of the patient (OR, PICU, or other) from the trauma bay is a decision that is based upon these factors. Frequent reassessments of the "ABCDs" of ATLS may help providers avoid secondary injury by preventing hypoxia and hypotension while treating evolving physiologic changes (e.g., developing intracranial hypertension).

Transport of the critically injured, intubated child is fraught with risks, and high-quality centers have established protocols to avoid problems (e.g., patient accompanied by provider with skills to re-intubate in case of accidental dislodgement of the ETT, pharmacologic agents to provide sedation/pain control/paralysis, equipment to suction and re-intubate, and oxygen). Endotracheal intubation, due to traumatic brain injury or other injuries, is a common indication for admission to the PICU. However, any patient may deteriorate and placement of higher-risk patients into a monitored setting may allow earlier recognition and treatment of any decompensation. Cooperation and communication between the trauma team and the PCCM team are critical in providing optimal care for these patients.

Ongoing management of the trauma patient involves frequent reassessments, optimizing the patient's hemodynamic status to maintain adequate perfusion, and providing nutrition within an appropriate timeframe. Understanding pediatric physiology and the physiologic response to injury is critical. Unlike many non-injured patients in the PICU (e.g., those with chronic lung disease or congenital heart disease), most injured children are otherwise healthy, with normal cardiopulmonary physiology at baseline. Shock in trauma patients is usually due to hemorrhage, except in the uncommon patient with neurogenic shock, and must be treated by control of the bleeding. Vasopressors, though providing temporary improvement in arterial pressure, will not provide primary treatment of the underlying cause of shock and should only be used in injured children until blood products are available and hemorrhage control can be obtained. Vasopressors should not be used without the knowledge of the trauma team. Hypothermia can be prevented by using warmed IV solutions (including use of high volume, rapid infusing devices, warmed blankets, and radiant warming lights). In extreme hypothermia, intracavitary warming (thoracic or peritoneal) may be used. Although studies have not demonstrated a neuroprotective effect of intentional hypothermia in brain injury patients, care should be taken to avoid hyperthermia.

45.4 Radiologic Imaging in Pediatric Trauma Patients

Guidelines that promote a reduction in radiologic imaging without sacrificing injury identification are important in evaluating injured children.

Over the last several years there has been increasing awareness of the long-term consequences of radiation exposure from medical imaging. These risks are greater in children. In many adult trauma centers, there is a reflexive response to "pan scan" most injured patients (CT scans of the head, face, cervical spine, chest, abdomen, and pelvis) to avoid missed injuries. Instead, a careful assessment of the benefits and risk of each study should be performed. Risks include unnecessary sedation, radiation, and contrast exposure. CT scans should be obtained for specific reasons based on symptoms and physical exam findings rather than in response to the mechanism of injury. CT scans of the chest and abdomen, if performed, should be obtained with IV contrast as this provides the greatest sensitivity for soft tissue injuries. CT scanning of children should always utilize the ALARA (As Low As Reasonably Achievable) radiation dose. Repeat CT scans should be reserved for specific clinical indications rather than ordered as a routine practice or protocol.

45.5 Evaluation of the Airway in a Multiply Injured Child

Concerns for airway compromise, including depressed GCS (≤8), or impaired breathing should prompt endotracheal intubation. Patients may be intubated by prehospital providers, but it is the responsibility of the Trauma Team Leader to confirm adequate position and function of the ETT once the patient arrives in the trauma bay. Expertise in pediatric intubation is a delineating feature of pediatric trauma centers; this expertise is provided by pediatric specialists in anesthesiology, emergency medicine, critical care medicine, and surgery. Intubation in a trauma patient can be complicated due to the need for cervical spine stabilization (i.e., the neck cannot be extended) and the possibility of blood or swelling obscuring airway visualization. Video laryngoscopy with fiber-optic cameras can be extremely helpful with the difficult airway, but the provider must be familiar with the equipment available in order to maximize the advantages. When airway patency cannot be achieved with bag mask ventilation or intubation, rescue maneuvers using either laryngeal mask airways (LMA) or needle cricothyroidotomy are appropriate alternatives. Surgical cricothyroidotomy is rarely necessary and should not be performed in a child <12 years old. If an emergency surgical airway is required in this age group, a tracheotomy is indicated.

45.6 Establishing Vascular Access in the Injured Child

Every injured child must have a secure airway and vascular access.

Appropriate vascular access is critical in severely injured children. A systematic approach should be established to avoid delays in the administration of fluid and medications. Lengthy attempts at peripheral access in unstable patients are unacceptable. Failed attempts at peripheral access should prompt placement of an intraosseous needle or percutaneous central venous access. Central line placement in children can be difficult, and surgical cutdown on the saphenous vein (groin in infants and younger children, ankle in older children) may be required by an experienced surgeon. Performing a venous cutdown for access should not delay attempts at intraosseous access. Access, whether peripheral or central, should be large bore and shorter lengths. An introducer sheath catheter, rather than a standard multi-lumen central line, is preferred due to the potential need for rapid, large-volume infusions.

45.7 Hemodynamic Monitoring as a Guide to Therapy in the Multiply Injured Child

The initial hemodynamic evaluation of an injured child consists of vital signs and a physical exam. Continuous telemetry and pulse oximetry, with automatic blood pressure measurements, are standard during the ongoing assessment and treatment of severely injured children. Knowledge of normal heart rate and blood pressure based on age is important in determining abnormal vital signs in children. The heart rate is influenced by multiple factors, such as pain, fear, and anxiety. Children can maintain adequate blood pressure until a loss of >30% of their blood volume, mandating frequent assessments of the patient rather than reliance upon reviewing the reported vital signs. A bladder catheter can aid in assessing the adequacy of resuscitation, though presence of pelvic injuries must be considered (e.g., blood at the meatus in a boy should raise concerns for a urethral injury, which requires evaluation by a urologist prior to attempting a catheter insertion).

Critically injured children are cared for in the PICU, where continued resuscitation may be required. Patients may be transferred to the PICU from the trauma bay for ongoing medical management or in order to stabilize the patient, prior to the OR, or postoperatively after emergent surgical procedures. Invasive monitoring devices, such as central venous catheters, arterial catheters, bladder catheters, and intracranial pressure monitors, may be employed depending upon the type of injuries sustained. Repeat blood draws are facilitated by arterial access and may be necessary for critically ill patients. The desire for frequent laboratory reassessments should be balanced with an understanding of the physiologic changes that occur after injury and the time that it takes for adjustments of medications and ventilators to impact laboratory values. Frequent blood draws can lead to clinically significant anemia, which can be particularly important in small children and lead to more frequent transfusions. The need for ongoing central access should be reconsidered daily due to the risk of central line-associated blood stream infections (CLABSI). Indwelling devices such as central venous and arterial lines should be removed as soon as medically possible.

45.8 Stabilization and Evaluation of the Axial Skeleton

All trauma patients are at risk for injury to the axial skeleton, and spinal precautions should be maintained until the spine can be "cleared" clinically and/or radiographically. Spine precautions include a properly fitting cervical collar and maintaining in-line positioning with log-roll only to move the patient. Patients may arrive on hard boards (this is becoming less frequent) but should be safely transferred to regular stretcher as soon as possible to avoid pressure complications. Cervical collars which are placed by EMS typically have minimal padding and should be changed to better padded collars as soon as feasible if the cervical spine cannot be cleared. Infants/toddlers between 1 and 3 years old have a disproportionate occipital prominence that results in flexion of the neck when lying on a flat bed. They should have a soft mat or padding (typically 1 inch) placed underneath their trunk to maintain a neutral neck position.

The entire spine should be stabilized during resuscitation and cleared using established guidelines.

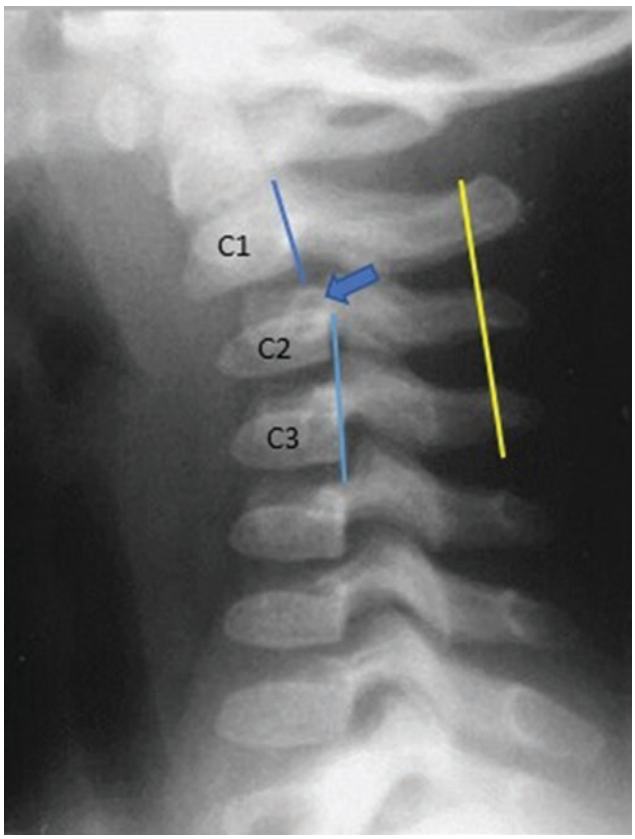
Cervical spine clearance should be standardized at each institution, balancing safety with practicality. The primary goal is to identify patients with unstable injuries for whom movement may cause or worsen spinal cord injury. Guidelines (NEXUS, Canadian C-Spine Rule) exist for cervical spine clearance without imaging in patients with low risk of injury, without distracting injuries (other painful injuries), who have a normal neurologic exam, and who have no cervical spine tenderness. Although these guidelines were developed for adult patients and have lower sensitivity and specificity in children, standardized protocols can be used safely to clear the cervical spine in many injured children without imaging. Although cervical CT scan has completely replaced standard radiographs in the evaluation of adult trauma patients, there is still a role for radiographs in children and many institutions have developed protocols to clear the cervical spine that minimize the need for CT scans in most injured children. The lateral cervical spine radiograph is useful for excluding significant spine fractures. Odontoid images can be difficult to obtain, particularly in young children, and have been abandoned at some institutions or limited to only children past a certain age. Protocols to limit CT scans may utilize MRI or discharge in a cervical collar and follow-up with a spine specialist before obtaining a CT scan. If there is a high suspicion for injury, or significant

tenderness, CT scans are still reasonable as these are more sensitive for bony injury than MRI, with MRI being more sensitive for ligamentous and spinal cord injury. Children are also at risk for spinal cord injury without radiologic abnormality (SCIWORA), in which standard radiographs and CT scans will be normal. Patients who have concern for SCIWORA should be evaluated by a spine specialist (neurosurgeon or orthopedic surgeon).

Cervical spine evaluation in children can be challenging due to injuries without radiographic abnormalities (SCIWORA) and radiographic irregularities without injury (pseudosubluxation, growth plates).

Pseudosubluxation presents a challenge in interpreting pediatric cervical spine radiographs. Anterior displacement of C2 on C3 (usually less than 4 mm) can occur in up to 40% of children under 8 years of age. It is due to the horizontal position of the facet joints at younger ages which leads to increased mobility of the cervical vertebrae. It is more apparent with the cervical spine flexed and resolves with the spine extended. The posterior cervical line (line of Swischuk) can confirm a pseudosubluxation and is drawn from the anterior aspect of the spinous process of C1 to the anterior aspect of the spinous process of C3. The anterior edges of the spinous processes of C1, C2, and C3 should line up within 1 mm of each other on both flexion and extension radiographs (◘ Fig. 45.1).

Thoracic and lumbar spine regions must also be evaluated and cleared in trauma patients. This can occur with physical exam in patients who are awake and cooperative. AP and lateral radiographs can exclude major injuries. CT scan should be reserved for patients with documented injuries seen on radiographs or those with a high suspicion of injury. In patients receiving a chest or abdomen CT scan, consider adding spine reconstruction images to the CT if there are protocols that allow both studies with no additional radiation exposure.



◘ **Fig. 45.1** Lateral radiograph demonstrating offset of C2 on C3 (blue arrow). Line of Swischuk (posterior cervical line, yellow line) transecting the anterior cortex of the spinous process confirms pseudosubluxation as the anterior cortices line up within 1 mm of each other. Courtesy F. Maffei

45.9 Supportive Care and Treatment for Cervical Spine Injury

Cervical spine injuries are rare in children (<2% of injured children), but all injuries mandate consultation by a spine specialist. Patients with a cervical spine injury may require a cervical collar for weeks to allow injuries to heal. Other patients may require surgery to stabilize fractures or ligament injuries in order to prevent spinal cord injury or worsening of an existing injury. Frequent log-rolling, padding pressure points, and attention to areas at high risk for pressure complications are essential for patients who are maintained in spine precautions due to injury, especially those with neurologic deficits or who have restricted movement or communication due to medical treatments, such as sedation for mechanical ventilation.

Neurogenic shock may occur in patients with injury to the upper spinal cord. This results from a loss of vasomotor tone. IV fluid administration and vasopressors are often both required to maintain adequate blood pressure and perfusion. There is insufficient evidence to support the use of steroids after spinal cord injury.

45.10 Supportive Care and Treatment for Chest Injuries

45.10.1 Chest Imaging

The primary imaging assessment for chest trauma is a simple AP radiograph, which is obtained in most trauma patients. Although CT scans provide much greater sensitivity in diagnosing injuries (e.g., pulmonary contusion or rib fractures), the clinical implications of these injuries that are not apparent on plain radiographs are marginal. CT scans are indicated when there is concern for injury to the aorta, as evidenced by widened mediastinum or loss of visualization of aortic edge (Fig. 45.2).

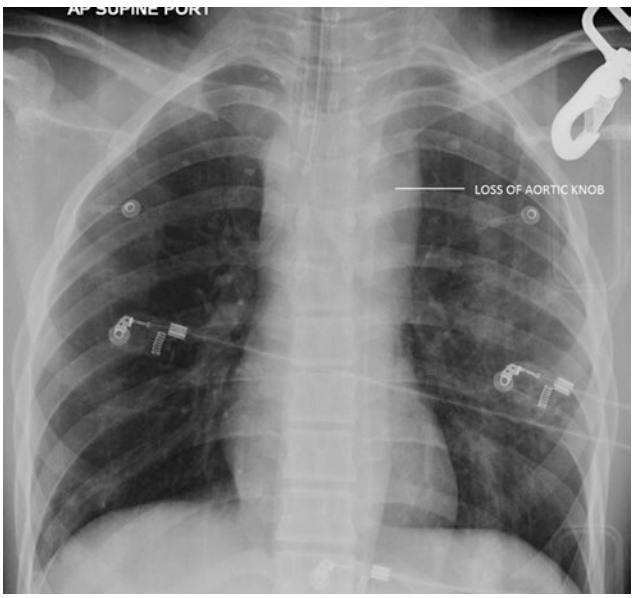


Fig. 45.2 Loss of aortic knob/edge from aortic dissection. Minimal widening of mediastinum

45.10.2 Pulmonary Contusion

Pulmonary contusions, especially when diagnosed only by CT scan, are common, though not often clinically significant.

Pulmonary contusions are the most common injury occurring in children after sustaining blunt thoracic trauma. Due to compliant cartilaginous ribs, children can sustain a pulmonary contusion without a rib fracture. Pulmonary contusions can be diagnosed by chest radiograph or CT. Most pulmonary contusions are not clinically significant and require no specific care. Severe pulmonary contusions, especially if bilateral, can lead to respiratory compromise, and some will require mechanical ventilation for supportive care while the contusion resolves. Respiratory effects from a pulmonary contusion may worsen over several hours due to the resulting inflammatory process that can lead to edema in the lung.

45.10.3 Pneumothorax/Hemothorax

Lung collapse due to intrapleural air (pneumothorax) or blood (hemothorax) is the second most common injury in blunt thoracic trauma. Traumatic pneumothorax and hemothorax usually require tube thoracostomy to drain air and or blood and allow lung re-expansion. A small "occult" pneumothorax, often only apparent on CT scan, is usually asymptomatic and requires no intervention beyond observation. Continued bleeding or uncontrolled air leaks (usually indicating an injury to the trachea or main bronchus) may require operative repair.

45.10.4 Rib Fractures

Flail chest is uncommon in children.

Rib fractures are the third most common injury in blunt thoracic trauma and usually require only supportive care with respiratory hygiene and pain control. Flail chest is an uncommon condition in children which occurs when at least three adjacent ribs are broken in at least two locations, allowing that segment of the chest wall to move paradoxically with the rest of the chest wall. This can result in respiratory compromise and may require mechanical ventilation and operative fixation of the rib fractures to stabilize the chest wall.

45.10.5 Injury to the Great Vessels

Many injuries to the great vessels are rapidly fatal, and these victims rarely survive to reach the hospital. Some injuries are not immediately fatal, and there is opportunity for patient salvage if diagnosed and treated promptly. Such injuries include dissection of the aorta and contained disruption of the aorta. The hallmark of such injuries is a widened mediastinum seen on chest radiograph, which can be difficult to confirm in younger children with a prominent thymus. A high index of suspicion is critical in diagnosing these injuries. CT scan with IV contrast has become the standard to diagnose such injuries (◘ Fig. 45.3).

Treatment for aortic arch injuries requires a cardiothoracic surgical consultation to determine if operative intervention is required. Operative repair may require cardiopulmonary bypass and anticoagulation. Management of these patients, especially those with multiple injuries, requires a multidisciplinary approach with close collaboration among specialties to prevent severe complications.

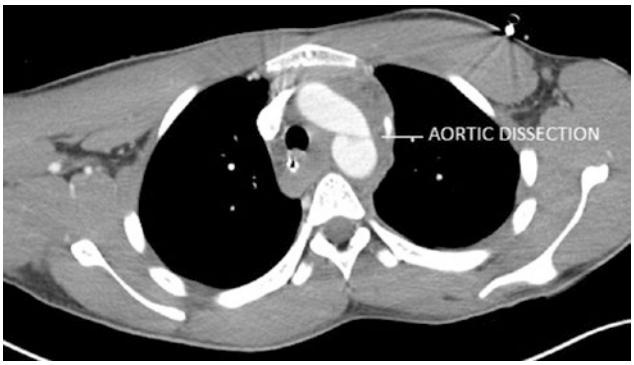


Fig. 45.3 Aortic dissection seen on CT angiogram of chest

45.11 Supportive Care and Treatment of Abdominal Injuries

Non-operative management of blunt injury to the spleen, liver and kidney has become standard except in cases of hemodynamic instability or ongoing bleeding.

Although any organ in the abdomen is susceptible to injury, the solid organs (spleen, liver, kidney, and pancreas) are most likely to be injured. Small children are predisposed to abdominal injuries because of the risk of visceral contents being forcibly compressed against the rigid spinal column. Mechanism of forcible compression of abdominal contents includes falls on bicycle handlebars and deceleration against a lap belt. Abdominal injuries are usually diagnosed by CT scan with IV contrast. FAST (Focused Assessment Sonography in Trauma), which has gained wide acceptance in adult trauma care for diagnosing abdominal/cardiac causes of traumatic shock, has more limited utility in injured children. The use of FAST in children varies by institution.

45.11.1 Spleen Injury

Most splenic injuries are caused by direct blow to the left upper quadrant or rapid deceleration forces (Fig. 45.4). Diagnosis is made by CT scan, and injuries are graded by severity using the American Association for the Surgery of Trauma (AAST) guidelines (Table 45.2). One important note about injury grading is that all grade criteria are based on adult patients (specifically the depth of injury); due to differences in sizes of organs in children, injury grading may underestimate the severity of injury in younger children.

Traditionally, treatment decisions were guided by grade of injury. However, utilizing hemodynamic stability rather than grade of injury to determine the need for surgical intervention has become the recommended approach. Using this approach, over 90% of children will not require surgery. In addition, ICU admissions (except for Grade V), length of bed rest, length of stay, and frequency of laboratory testing are reduced. Operative intervention is typically reserved for children with hemodynamic instability despite resuscitation or who have ongoing transfusion requirements of more than 50% of estimated blood volume. Embolization of the splenic artery (or segmental branch) is another option for patients who are stable but have evidence of ongoing bleeding. This is more feasible in older children who have greater diameter vessels and requires an interventional radiologist experienced in this mode of treatment in children. Active extravasation of IV contrast (a "blush" on CT) may raise concern for ongoing bleeding risk but is not by itself an absolute indication for intervention.

Patients who require surgery should have a direct repair (splenorrhaphy) or partial splenectomy when possible. Full splenectomy may be required to obtain hemodynamic stability. Post-splenectomy treatment must include immuniza-

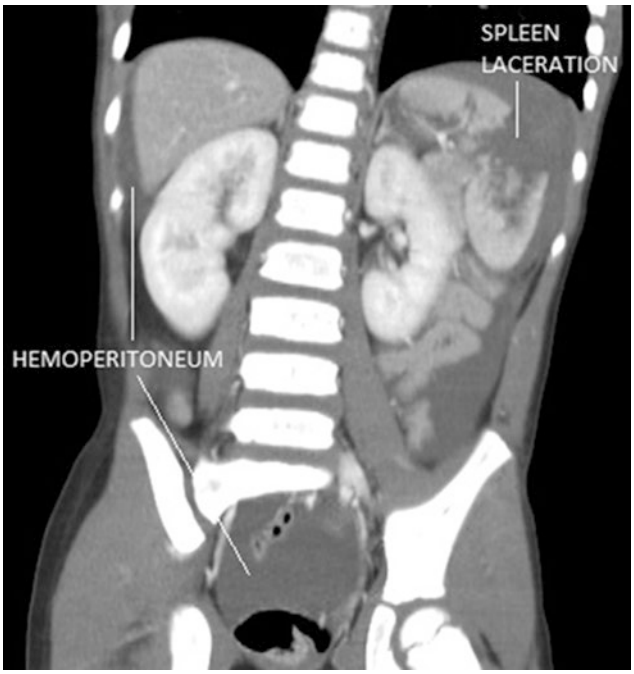


Fig. 45.4 Laceration of spleen with hemoperitoneum

Table 45.2 AAST Grading system for traumatic spleen injuries

Grade	Description
I	Subcapsular hematoma, <10% surface area
	Laceration <1 cm depth
II	Subcapsular hematoma, 10–50% surface area
	Intraparenchymal hematoma, <5 cm diameter
	Laceration 1–3 cm depth not involving trabecular vessel
III	Subcapsular hematoma >50% surface area, expanding, or ruptured
	Intraparenchymal hematoma ≥5 cm or expanding
	Laceration >3 cm depth or involving trabecular vessel
IV	Laceration involving segmental or hilar vessel producing devascularization of >25% of spleen
V	Completely shattered spleen
	Hilar vessel injury with devascularized spleen

Originally reported by Moore EE, et al. Organ injury scaling: spleen and liver. J Trauma. 1995;38(3):323–4. Used with permission

tions (pneumococcal, meningococcal, *Haemophilus* influenza). Antibiotic prophylaxis with penicillin is often performed, though there are no national guidelines regarding antibiotic prophylaxis duration. Immunizations are scheduled at least 2 weeks after surgery according to the guidelines set forth by the Centers for Disease Control. There is a lack of consensus on recommendations for resuming full activity after blunt splenic injuries. Patients who are managed without surgery are typically restricted from sports for 3–6 weeks based on injury severity.

45.11.2 Liver Injury

Liver injuries are managed in a manner similar to spleen injuries and are also graded according to AAST guidelines (Table 45.3). Operative management for bleeding may identify life-threatening hemorrhage that may require "damage control" surgery, where the abdomen is packed with sponges to tamponade bleeding in order to allow time for resuscitation in the ICU before attempting definitive management of injuries. Early activation of a massive transfusion protocol (MTP), which uses an appropriate ratio of blood products (PRBC, platelets, FFP, cryoprecipitate), is critical in such situations to maintain acceptable hemoglobin levels while treating coagulopathy and thrombocytopenia which inevitably develop. Thromboelastography and thromboelastometry are newer techniques that analyze the components of clot formation and dissolution and allow a more focused correction of acquired coagulopathies.

Leak of bile from damaged intrahepatic bile ducts may develop several days after an injury and usually manifests as severe abdominal pain and tenderness. Such injuries may require a multidisciplinary treatment plan, including pediatric surgeons for laparotomy/laparoscopy to wash out the abdomen in diffuse peritonitis and place drains, radiologists to use image-guided drainage of contained leaks, and gastroenterologists to perform endoscopic retrograde cholangiopancreatography (ERCP) with possible sphincterotomy and stent placement to reduce the pressure in the biliary system and allow better drainage into the duodenum.

45.11.3 Kidney Injury

Kidney injuries are also graded according to AAST guidelines (Table 45.4). Kidney injuries occur less commonly than liver or spleen injuries and there is less evidence regarding a standard management approach. Re-imaging of

Table 45.3 AAST Grading system for traumatic liver injuries

Grade	Description
I	Subcapsular hematoma <10% surface area
	Laceration <1 cm depth
II	Subcapsular hematoma 10–50% surface area
	Intraparenchymal hematoma <10 cm diameter
	Laceration 1–3 cm depth, <10 cm length
III	Subcapsular hematoma >50% surface area or ruptured
	Intraparenchymal hematoma >10 cm or expanding
	Laceration >3 cm depth
IV	Parenchymal disruption involving 25–75% of hepatic lobe or 1–3 Couinaud's segments within a lobe
V	Parenchymal disruption involving >75% of hepatic lobe or >3 Couinaud's segments within a lobe
	Juxtahepatic venous injury (e.g. retrohepatic IVC)
IV	Hepatic avulsion

Originally reported by Moore EE, et al. Organ injury scaling: spleen and liver. J Trauma. 1995;38(3):323–4. Used with permission

Table 45.4 AAST Grading system for traumatic kidney injuries

Grade	Description of Injury
I	Contusion, microscopic or gross hematuria with normal imaging
	Subcapsular hematoma, nonexpanding and without parenchymal injury
II	Nonexpanding perirenal hematoma confined to retroperitoneum
	Laceration <1 cm depth without urinary extravasation
III	Laceration >1 cm depth without collecting system rupture or urinary extravasation
IV	Laceration extending through cortex, medulla, and collecting system
	Main renal artery or vein injury with contained hemorrhage
V	Completely shattered kidney
	Avulsion of renal hilum which devascularizes kidney

Originally reported by Moore EE, et al. Organ injury scaling: spleen, liver and kidney. J Trauma. 1989; 29(12):1664–6. Used with permission

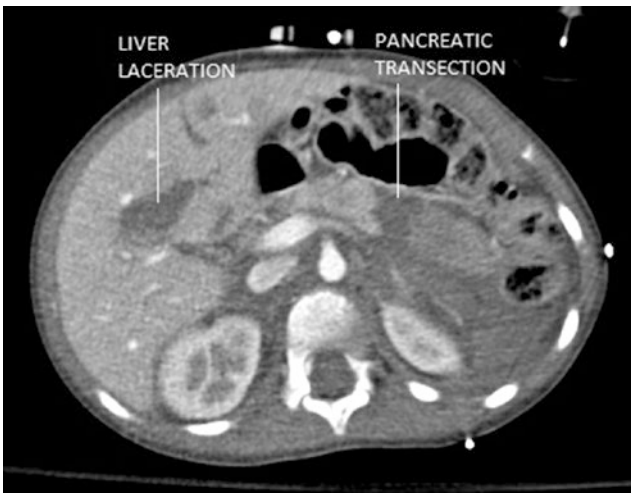


Fig. 45.5 Complete transection of pancreas and liver laceration. Typical pancreatic transection overlies the vertebral body, with this injury being slightly more distal than typical

high-grade kidney injuries is common and is used to evaluate for ongoing urine leak from the collecting system. Urinomas may be drained via ureteral stenting or percutaneously and require participation of urologists in the management of the patient. Most patients with kidney injuries, even high-grade injuries, can have renal salvage. Indications for immediate operation are usually ongoing bleeding, hemodynamic instability, or high-grade penetrating injury.

45.11.4 Pancreas Injury

Many pancreatic injuries, such as contusions and partial-thickness lacerations, usually heal with non-operative management. Complete transection of the pancreatic duct (Fig. 45.5), usually at the mid-body of the pancreas overlying the vertebral bodies, is more frequently being treated with distal pancreatectomy. This can often be performed laparoscopically and may be done up to

3 days after injury. MRCP and ERCP may be helpful in determining the presence of a pancreatic duct transection. Severe injuries to the head of the pancreas are, fortunately, rare, but may require extensive surgery (e.g., a Whipple pancreaticoduodenectomy) for definitive treatment.

45.11.5 Intestine Injury

In blunt trauma, intraperitoneal fluid in the absence of solid organ injury should raise suspicion of intestinal perforation.

Intestinal injuries in the setting of blunt abdominal trauma are uncommon and can be difficult to diagnose. Blunt mechanisms associated with intestinal injury include a fall from bicycle and landing on the end of the handlebar or a motor vehicle collision with lap-belt flexion (patients with a "seat belt sign"). A high riding lap belt without the use of a shoulder strap can cause severe flexion upon deacceleration and/or impact. Injuries to the intestine and spinal column can occur concomitantly. A Chance fracture is a transverse fracture through the anterior, middle, and posterior elements of the spine. This fracture most commonly occurs at the thoracolumbar junction in adults but can be observed in the mid lumbar region in children. Neurological deficit is uncommon but occurs more frequently in children than adults. Of note, the incidence of concurrent intra-abdominal injuries, especially intestinal and pancreatic injury, can be as high as 50%.

Intra-abdominal fluid in the absence of a solid organ injury can raise suspicion for intestinal injury but is non-specific. Free air visualized on CT scan is nearly pathognomonic but is often absent on initial CT scan if obtained shortly after the accident. If there is concern for intestinal injury, observation with serial exams and diagnostic laparoscopy are both acceptable. Serial assessments should occur every 2–4 h and include vital signs and physical examination. If there is deterioration in the evaluation (e.g., fever or increasing pain), surgery is indicated. Intestinal injuries require surgery for treatment; most intestinal injuries, even of the colon, can be repaired primarily without placement of an ostomy if identified early and other injuries would not compromise the repair. Penetrating injuries to the abdomen, except in very specific situations (e.g., stab without peritonitis), require laparotomy and repair of intestinal injuries identified.

45.12 Special Problems Associated with Orthopedic Injuries

45.12.1 Fat Embolism Syndrome

Fat embolism syndrome (FES) is rare and typically associated with long bone (primarily femur) or pelvic fractures. It may occur after orthopedic manipulation to treat the fractures. Patients may develop a triad of symptoms which include hypoxia, neurologic deterioration, and a petechial rash. None of these features are specific for FES and not every patient will develop all three symptoms. The petechial rash is the least common symptom. Symptoms may not develop for 1–3 days after the injury. FES is a clinical diagnosis and requires a high level of suspicion and care is supportive.

45.12.2 Compartment Syndrome

The diagnosis and treatment of compartment syndrome should occur before signs of ischemia are present.

Compartment syndrome (CS) occurs when pressure within the tissues in an anatomic compartment (bounded by fascia) exceed intravascular pressure, which results in decreased perfusion and subsequent ischemia of those tissues.

This usually occurs in the tight compartments of the leg, arm, or forearm. Common mechanisms include fractures, crush injuries, and vascular injuries that result in prolonged ischemia. Classically, CS presents with the "5 Ps" – pain, pallor, paresthesia, paralysis, and pulselessness. Pain is constant but may be worsened with passive movement that flexes/extends a muscle in the affected compartment. Lack of pulses is a late sign of compartment syndrome, and the diagnosis should be made prior to the onset of pulselessness. The diagnosis can be made by clinical assessment or measuring the compartment pressure directly. Treatment includes fasciotomy of all affected compartments in that region of the body (e.g., the four compartments in the leg); the skin is usually left open due to the severe edema of the tissues and skin grafts are often required. The diagnosis and treatment must occur early to prevent permanent disability.

45.12.3 Hemorrhage

Although severe bleeding from a fracture is rare, hemorrhage associated with femur and pelvic fractures can be severe and life-threatening. The thigh can accommodate a large volume of blood within its tissues, and the thigh is one of the "hidden" compartments to assess if a patient has unexplained hemorrhagic shock. This is especially true in small children. Pelvic fractures, with injury of surrounding blood vessels, can also cause severe hemorrhage that can be difficult to control. A pelvic binder applied in the trauma bay can help tamponade bleeding from pelvic fractures and should be considered in the unstable pelvis; a sheet, wrapped around the pelvis and tightened, can be used if no commercial product is available. External fixation of the fractures may be needed to avoid entering the areas of the hemorrhage around the bones.

45.13 Deep Venous Thrombosis and Pulmonary Embolism

There is increasing awareness of the risk of deep venous thrombosis in injured children, particularly adolescents, and the association of DVT with central venous catheters. The risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) is low in children, but the risk increases with the age of the child. The highest risk seems to be in postpubertal patients or those over 15 years. There is very limited data regarding the prevention of DVT and PE in pediatric patients. Mechanical compression devices are rarely used in small children but may be used in adolescents. Chemical prophylaxis (usually low-molecular-weight heparin products) can be safely used if there are no contraindications (e.g., intracranial hemorrhage), and should be considered in adolescent patients, especially if they will have a prolonged time of being bedbound or have high risk injuries, such as pelvic fractures. Although guidelines have recently been developed for DVT prophylaxis in pediatric trauma patients, these guidelines are based on evidence from adult patients as there is limited evidence available for children.

45.14 Approach to the Injured Child Who May Be the Victim of Non-accidental Injury

Child abuse is a significant cause of death and morbidity in children and is the most common cause of serious head trauma in children less than 1 year. Child abuse occurs in children from all socioeconomic, racial, and cultural groups. Physicians must maintain a high index of suspicion to identify child abuse,

Physical child abuse should be suspected if injury patterns are inconsistent with the history provided, changing history, or a delay in seeking treatment.

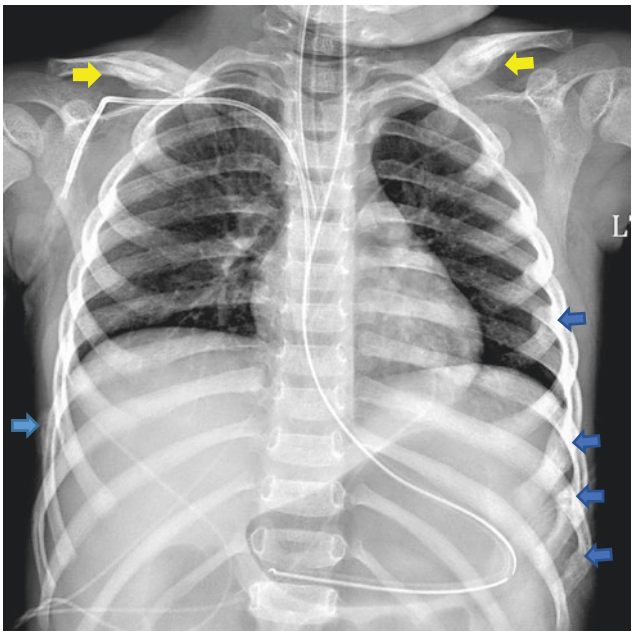


Fig. 45.6 Initial chest radiograph in a 3-year-old with history of seizure after a short fall. Child presented in respiratory failure and decompensated shock. Findings include endotracheal tube at level of the carina and right subclavian catheter tip in the right atrium. Most importantly, multiple healing bilateral rib fractures are present (blue arrows) and healing midshaft fractures of both clavicles (yellow arrows)

since it is rare that a parent will report that their child has been abused, even if that abuse is by someone other than the parent. Child abuse is suspected based on the types of injuries and the history provided by the parents/caregivers. Often a history is given of a trivial mechanism of injury (short fall) that is inconsistent with the severity of physiologic derangements (Fig. 45.6). Suspicion should be raised if there are discrepant histories of how the injury occurred, delay in seeking medical care, injuries of varying ages (especially if only one mechanism is given), injuries inconsistent with the mechanism described, and injuries inconsistent with the developmental/physical age of the child (e.g., bruising in an infant who cannot roll over or a fracture in a child who cannot walk). Regardless of the concern for abuse, the priority for these patients is the treatment of their injuries, and their initial assessment follows ATLS guidelines as for other trauma patients.

Evaluation of patients with suspected non-accidental injury should involve a pediatrician with training in child abuse. Protocols for such evaluations should be developed to avoid allowing individual, and often unconscious, bias to enter the evaluation process. Photographic documentation of injuries can be critical for use in criminal proceedings. Those documenting in the medical record should be aware that such records will likely be used in legal proceedings, and documentation should be accurate without making guesses or speculation regarding perpetrators or mechanisms of injury. Each state has mandatory reporting laws; physicians and other healthcare providers should familiarize themselves with the laws in the states where they work. The evaluation of these patients requires coordination between hospital staff, government agencies, and law enforcement; child abuse pediatricians often provide an expertise in these interactions and often serve as a liaison between the healthcare team and the government investigators.

45.15 Head Injury

45

Severe brain injury has worse outcomes when associated with hypoxia or hypotension.

For a more detailed discussion of head injury, please refer to ▶ Chap. 25. Treatment of a patient with a severe head injury begins with the arrival of first responders at the scene of the accident. Patients with severe head injury

(usually GCS ≤ 8) require intubation. Establishing and maintaining a stable airway and providing oxygen are critical treatments in a child with a severe brain injury. Outcomes with severe brain injury are worse in patients who have hypoxia or hypotension. Treatment upon arrival at the trauma center includes confirmation of airway, mechanical ventilation, and hemodynamic support with fluids, blood products, and vasoactive medications, if needed. Hypotension is not caused by brain injury; if hypotension is present, the cause must be sought and treated. Minor procedures, such as laceration closure, can be delayed until reaching the PICU unless there is profuse bleeding (e.g., a large scalp laceration). Hyperosmolar therapy (mannitol or hypertonic saline) may also be indicated; mannitol should not be used in the setting of hypotension as it has a diuretic effect that can worsen hypotension. Neurosurgery should be promptly consulted to assist with the assessment and management.

Patients with severe head injury should be transferred to the PICU once their initial evaluation and imaging are complete. Patients with other life-threatening injuries may require operative intervention prior to admission to the PICU; treatment of the head injury with medical management should continue in the operating room and is managed by the anesthesiology team. Supplemental monitoring, such as arterial access and intracranial pressure monitoring, may be helpful and can be performed in the operating room or the PICU. The pediatric critical care team has an important role during the early assessment and treatment of these patients, and communication between the trauma surgeon, pediatric intensivist, neurosurgeon, and anesthesiologist is essential. Hospitals that care for trauma patients should have protocols developed for the management of severe head injuries, including neuroprotective strategies and escalation of care plans, that have been agreed upon by the involved physician teams to avoid confusion, miscommunication, and variabilities in management based on personal experience or opinion.

45.16 Initial Evaluation, Fluid Resuscitation, and Care of the Severely Burned Child

Burns are common causes of injury in the United States. More than 300 children receive medical care for a burn each day, and over 700 children die from burn injuries annually in the United States. Initial evaluation of a burn patient is similar to that for other trauma patients, with additional emphasis on problems that are unique to burn victims. Delineating the mechanism of burn and a thorough head-to-toe assessment are crucial to avoid missed injuries. For example, one might expect different injuries if the burn was associated with an explosive device, a house fire that led to the child jumping from an upper floor window, or a motor vehicle collision.

45.16.1 First Priorities

ATLS protocols should be followed during the initial assessment of a burn victim. Evaluation for inhalation injury should be included in the airway assessment, since edema may develop over time and make intubation difficult if delayed. Burns around the mouth, face, or neck, soot or other burn debris in the mouth, carbonaceous sputum, or report of the patient being in an enclosed burn environment should prompt consideration for intubation. Stridor or cir-

cumferential burns to the neck are high-risk indicators. All clothing must be removed. Chemical burns must be carefully evaluated, removing the chemical agent while also protecting medical personnel from contact with that agent. IV access must be obtained, even if the catheter must be placed through burned skin. Clean, dry linens are used to cover the patient, and sterile gauze can be used to cover or loosely wrap wounds. Burns should be assessed for depth and total body surface area (TBSA). In the rare setting of circumferential, deep burns, escharotomy can be life- or limb-saving and should be performed promptly. Narcotics and sedatives are used as needed. Agitation and restlessness may be signs of hypoxia or shock.

45.16.2 Carbon Monoxide Poisoning

Patients who sustain a burn by fire, especially if in an enclosed space (house or car fires), are at risk for carbon monoxide (CO) poisoning. Most immediate fatalities in burn victims are due to CO poisoning. Carbon monoxide has 200 times the affinity for hemoglobin as oxygen. Pulse oximetry cannot distinguish between oxygenated hemoglobin and carboxyhemoglobin (COHb) and is falsely elevated in this setting. Arterial blood gas, including measurement of COHb, is essential in these patients. All patients should have 100% oxygen via non-rebreather face mask or endotracheal tube administered until the CO and paO_2 levels are known. CO is eliminated 4–5 times faster with 100% oxygen compared to room air. The role of hyperbaric oxygen is controversial and only available at a limited number of centers. Other noxious gases can be produced in fires, especially industrial fires, and these can add to the lung injury. Cyanide poisoning should be considered if there is persistent metabolic acidosis, apnea, or depressed level of consciousness after adequate resuscitation.

45.16.3 Types of Burns and Extent of Burn Injury

Burn depth is traditionally separated into first, second, or third degree; however, describing thickness of burns may be more clinically relevant (Table 45.5). First-degree burns are superficial, involving only the epidermis. They are erythematous, blanch, and are painful. First-degree burns rarely require treatment and do not factor into TBSA of the burn for fluid resuscitation. Second-degree, or partial-thickness, burns involve the dermis and are characterized by erythema and blisters. These are also painful. Third-degree, or full-thickness, burns involve the entire depth of skin. The skin appears leathery, is usually pale, and is relatively painless due to destruction of the sensory nerves to the skin. Deeper burns involving the subcutaneous tissues that extend to muscle, tendon, and/or bone have been termed "fourth-degree" burns. It is important to realize that the differences between second- and third-degree burns are not as distinct as often taught; "deep" second-degree burns may require treatment like a third-degree burn. The depth of injury may also "progress" or become more obvious over time, such that a burn initially classified as first or second degree may subsequently be identified as second or third degree. Fluid resuscitation is based on the total combined surface area of the second- and third-degree burns. The "rule of nines" can be adapted to infants and children, and such charts are useful to rapidly calculate the TBSA (Fig. 45.7). Treatments for burns may include topical wound care, debridement, and skin grafting.

Table 45.5 Burn classification table

Degree classification	Thickness classification	Depth of injury	Characteristics	Treatment priorities
First	Superficial	Epidermis	Pain, red, mild edema	Pain control
Second	Partial	Superficial dermis	Pain, blisters, severe edema	Pain control Fluids as needed Protective covering Debridement as needed
Third	Full	Complete dermis, subcutaneous fat	Relatively painless, white, leathery	Pain control ABCDE Fluid resuscitation Protective covering Debridement Grafting if needed
Fourth	Full	Subcutaneous fat, muscle, bone	Insensate, charred	Life and limb salvage ABCD Fluid resuscitation Limb reconstruction and grafting

45.16.4 Fluid Resuscitation

Resuscitation of burn victims can require very large volumes of isotonic intravenous fluids.

Extensive burns can cause a severe inflammatory response that results in loss of intravascular volume. Large volumes of isotonic fluids are required to make up for these losses, and resuscitation should be started during the initial evaluation. Adequate fluid resuscitation can minimize secondary injury from poor perfusion. The goal of resuscitation is a urine output of 1–1.5 mL/kg/h. Patients with TBSA >20% should receive formal fluid resuscitation. The Parkland formula was traditionally used to guide initial fluid requirements, with the initial 24-h fluid requirement being 4 mL/kg/% TBSA in addition to maintenance fluids. The American Burn Association currently recommends 2–4 mL/kg body weight/% TBSA of fluid be given over the first 24 h; half of this volume is given during the first 8 h and the remainder during the next 16 h. The most commonly used fluid is lactated Ringer's. This fluid resuscitation is in addition to the maintenance needs of the child. These fluid requirements will seem extraordinarily large to those not familiar with burn resuscitation (e.g., a 20 kg child with 50% TBSA burn may receive 4 mL × 20 kg × 50 = 4000 mL/24 h, with a rate of 250 mL/h for the first 8 h, in addition to the 60 mL/h maintenance rate).

45.16.5 Criteria for Transfer

After initial evaluation and the initiation of treatment, a decision must be made regarding transfer to a burn center. The American Burn Association criteria for transfer are summarized in Table 45.6. Phone consultation with a

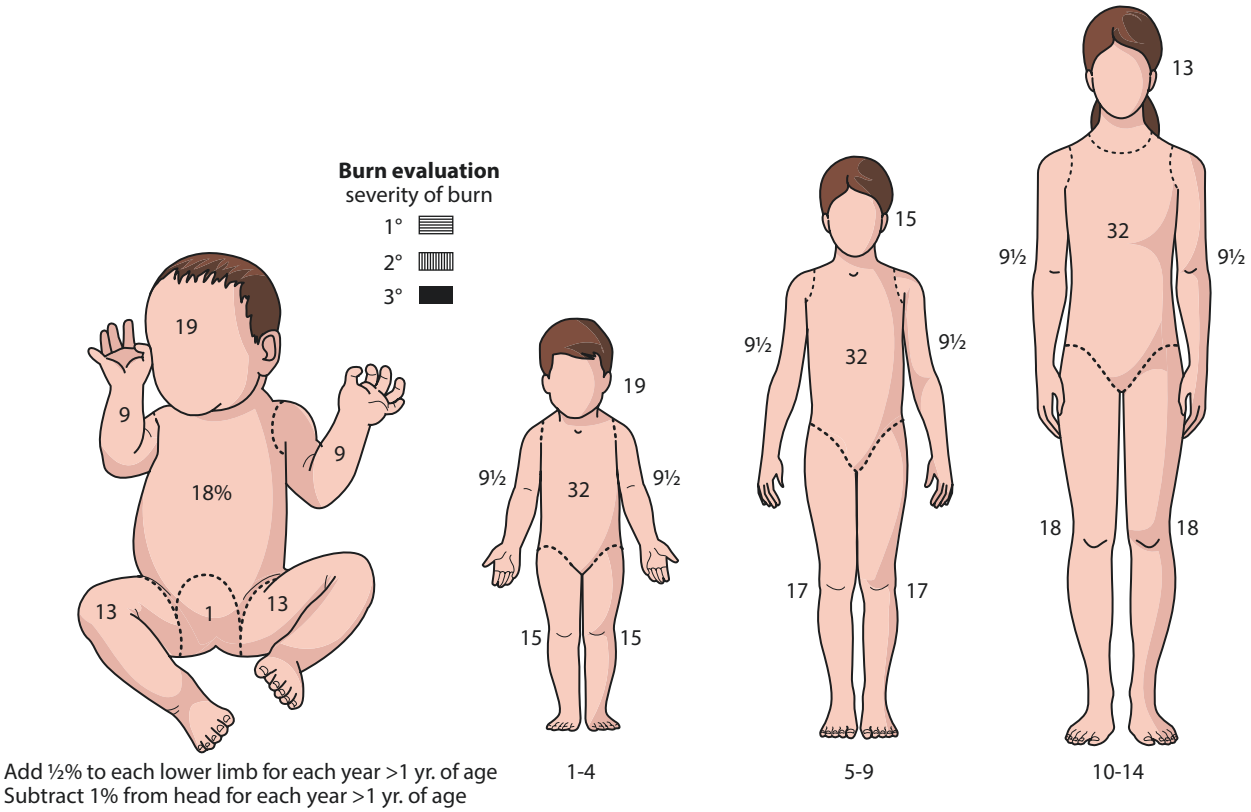


Fig. 45.7 Example of burn chart adjusted by age

Table 45.6 Chart adapted from: American College of Surgeons Committee on Trauma. Resources for the optimal care of the injured patient. 6th ed. 2014. Used with permission

Burn center referral criteria	
Partial thickness >10% total body surface area	Inhalation injury
Burns involving face, hands, feet, genitalia, perineum, or major joints	Burn injury with preexisting medical conditions that could complicate management
Third-degree burns in any age group	Burns with concomitant trauma in which the burn poses that greatest risk of morbidity and mortality
Electrical burns, including lightening	Burned children in hospitals without qualified personnel or equipment to care for children
Chemical burns	Burn injury in patients with special social, emotional, or rehabilitative interventions

burn specialist may also be helpful in determining the need for transfer. Many burn centers are now adopting "teleburn" technology with referring hospitals that allows the burn specialist to remotely view the patient and their burn injuries to provide recommendations regarding initial management and decision for transfer.

45.17 Summary

Pediatric trauma centers can improve the outcomes in severely injured children. Most pediatric traumas occur as a result of falls, motor vehicle collisions, or being struck by a vehicle/object. A high-functioning PICU with pediatric critical care medicine specialists plays a crucial role in optimizing the short- and long-term outcomes of these patients. A "concurrent" model of care, where the pediatric trauma surgeon and pediatric intensivist work closely together in the care of injured children, is a model that serves the best interest of these children. ATLS protocols are used during the initial evaluation of injured children, and physicians providing care for injured children should understand the concepts and strategies of ATLS and preferably be ATLS-certified. The ABCs are assessed and treated first, including confirmation of a secure airway and obtaining vascular access. The axial skeleton is initially stabilized and then "cleared" based on clinical and radiologic criteria. Multisystem injuries are treated by multidisciplinary teams, with the trauma surgeon prioritizing and coordinating the care. After initial assessment and initiation of treatments, transfer should be considered for burn victims who meet criteria or for general trauma patients if the hospital providing the initial evaluation is not a pediatric trauma center.

Review Questions

1. During initial evaluation of a pediatric trauma patient, the first and foremost responsibility is which of the following?
   A. To assure appropriate warming of the patient
   B. To obtain secure vascular access
   C. To confirm the adequacy of the airway
   D. To identify any injuries requiring emergent intervention
   E. To maintain crowd control and facilitate a coordinated team effort

2. Which of the following statements is true regarding the management of spleen trauma?
   A. Patients for whom blood replacement requirements exceed 50% of their total blood volume will likely require surgery.
   B. Grade IV spleen injuries are characterized by a "shattered" spleen or hilar vascular injury.
   C. If surgery is needed, splenectomy is preferred over splenorrhaphy due to the risk of continued bleeding.
   D. In children requiring splenectomy, antibiotic prophylaxis is recommended, but pneumococcal vaccination is not required.
   E. Non-operative management is successful in <60% of patients.

3. Which of the following intra-abdominal injuries cannot be treated without an operation?
   A. Liver lacerations
   B. Pancreas injuries
   C. Kidney lacerations
   D. Small bowel injuries
   E. Spleen lacerations

4. Which of the following is the most correct regarding pseudosubluxation of C2 on C3?
   A. It is predominately seen in children with Down syndrome (trisomy 21).
   B. It is caused by lack of fusion of vertebral ossification centers.
   C. It can be confirmed by assessing the posterior cervical line (line of Swischuk).

D. It requires internal fixation to avoid spinal injury.
E. It is associated with severe flexion injuries.

5. A 16-year-old male was involved in a motor vehicle collision in which he sustained a right femur fracture and pelvic fractures. He sustained no other obvious injuries, had no loss of consciousness, had a normal chest radiograph on initial evaluation, and had no abdominal pain. He has been awake and appropriately interactive. He is taken to the operating room the day after injury for open reduction and internal fixation of his fractures. Postoperatively, he becomes acutely hypoxic, confused, and combative. Given the most likely explanation of his symptoms, what other finding may be evident on physical exam?
   A. Absence of a pulse in the right foot
   B. Absence of breath sounds on the right
   C. Anisocoria
   D. Heart murmur
   E. Petechiae

6. A 5-year-old girl sustains a fracture to the right tibia and fibula when it is run over by a tractor tire. She underwent open reduction and internal fixation, with application of a cast, on the same day as the injury. The next day she complains of increasing pain in the leg that is not responding to the pain medications already ordered, prompting repeated calls from the patient's nurse. The MOST appropriate response is which of the following?
   A. Order radiographs of the leg to exclude malalignment of the fracture.
   B. Assess the perfusion of the foot and contact the orthopedic service to assess for compartment syndrome.
   C. Assure the nurse that increasing pain after this type of surgery is common and usually due to the effects of anesthesia wearing off.
   D. Increase the dose of pain medications, including narcotics, until the pain is improved.
   E. Take off the cast and order a vascular duplex to assess for venous thrombosis.

7. Lack of a pulse is an early sign in the progression of compartment syndrome. True or False?
   A. True
   B. False

8. Which of the following statements is true regarding the pediatric burn patient?
   A. Fluid resuscitation should be performed with 0.45 normal saline to account for third-space losses and to prevent hypernatremia.
   B. Most immediate fatalities from fire-related burns result from carbon monoxide poisoning.
   C. Surgical escharotomy should only be performed at an accredited burn center.
   D. Priorities for burn resuscitation focus on evaluation and treatment of the burned tissue rather than ATLS protocols.
   E. Third-degree burns are extremely painful and red with blisters.

9. A 5-year-old, 25 kg boy was involved in a house fire and sustained partial-thickness burns of 20% of his body and full-thickness burns to an additional 30% of his body. He is hemodynamically stable and IV access was just obtained. You decide to use the Parkland formula for fluid resuscitation. Which of the following most closely identifies the volume of fluid (resuscitation and maintenance) to give in the first 24 h?

A. 2600 mL
B. 4000 mL
C. 5600 mL
D. 6600 mL
E. 8000 mL

10. A 3-week-old female is admitted to the PICU with a traumatic brain injury after it is reported that she rolled from a changing table onto a carpeted floor. Which of the following is NOT an appropriate action?
A. Consultation by neurosurgery
B. Documenting in the medical record that the severity of injury is consistent with the mechanism given
C. Documenting the injury in the medical record quoting the radiology report
D. Consultation by child abuse pediatricians to assess for physical child abuse
E. Contacting the appropriate government authorities in accordance with mandatory reporting laws of the state

Answers

1. C
2. A
3. D
4. C
5. E
6. B
7. B
8. B
9. D
10. B

Suggested Reading

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Toxicology for the Pediatric Intensivist

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Contents

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Learning Objectives

- Understand the epidemiology of pediatric poisonings.
- Appreciate unique pediatric considerations when approaching the poisoned child.
- Understand the important points in the history, physical examination, and laboratory evaluation of the poisoned child, including the recognition of a "toxidrome."
- Describe the limits and benefits of toxicological drug screening and quantification of specific toxins.
- Understand key management strategies in treating the poisoned child within the context of position statements of the *American Academy of Clinical Toxicology* and *European Association of Poisons Centres and Clinical Toxicologists*.
- Review toxic ingestions of importance to the pediatric intensivist.

46.1 Epidemiology

Most pediatric toxic ingestions are benign; however, 3.5% result in moderate to severe effects.

The American Association of Poison Control Centers reports over two million cases of poisonings annually with nearly 50% of exposures occurring in children less than 6 years of age. Fortunately, most accidental pediatric ingestions are relatively benign with only 3.5% of children experiencing moderate to severe toxin-related effects. Fatality from poisoning represents approximately 0.01% of annual exposures. Pediatric poison exposures and mortality have declined due to preventive education, the development of poison control centers, safer childproofing techniques, and improved therapies when toxic ingestions occur.

There is a bimodal age distribution of pediatric poisonings. The initial peak occurs between the ages of 1 and 2 years with a male predominance. Exposures in this age group are most often inadvertent and involve substances commonly found around the home and include personal care products, household cleaning items, medications, and foreign bodies. The second peak of exposures occurs in adolescence. These exposures are often intentional due to suicide attempt or illicit drug use. Females are more likely than males to attempt suicide by toxic ingestion.

A bimodal age distribution of pediatric poisonings exists with the initial peak in the toddler years often due to accidental ingestion and the second peak in adolescence due to suicide attempts and illicit drug use.

Most toxic exposures usually involve one substance. Greater than 90% of ingestions occur in the home. Enteral ingestion is the most common route of poisoning (84% of cases). The inhalational, dermal, and ophthalmic routes each account for approximately 5% of toxin exposures. Recently, buprenorphine and clonidine have become the most common causes of ingestional hospitalizations.

Due to the prevalence of childhood toxin exposure and the need for prompt recognition and treatment, the intensivist must maintain clinical competence in the management of the severely poisoned child or adolescent.

46.2 Pediatric Considerations

Certain commonly prescribed medications possess a high risk for fatal overdose in children due to their narrow therapeutic window.

Toddlers are at increased risk for potentially fatal overdoses due to their relatively small size and the narrow therapeutic window of some commonly available medications. ◘ Table 46.1 provides an overview of commonly available substances that have the potential for causing severe toxicity after small ingestions.

Table 46.1 Fatal in small doses

Substance	Potentially fatal dosage (MG/KG)	Maximal unit dose available	Potentially fatal amount (10 kg child)	Toxicity
Tricyclic antidepressants Imipramine Desipramine	15	150 mg 75 mg	1 tablet 2 tablets	Anticholinergic effects, cardiovascular effects (arrhythmia, hypotension), central nervous system effects (coma, seizures)
Chloroquine Hydroxychloroquine	20	500 mg 200 mg	1/2–1 tablet 1 tablet	Gastrointestinal and central nervous system effects followed by severe cardiotoxicity (hypokalemia, hypotension, vasodilatation, QRS prolongation)
Diphenoxylate/ atropine (*Lomotil*)	1.25	0.025 mg atropine + 2.5 mg diphen/5 mL or tablet	4 tablets	Atropinism (dry mouth, tachycardia, flushing, mydriasis, hyperpyrexia) with delayed opioid effect (central nervous system and respiratory depression)
Camphor (*VapoRub*, *Campho-Phenique*)	100	1 g/5 mL	1 tsp. of pure liquid, 2 swallows of *Campho-Phenique*, 4 mouthfuls of *VapoRub*	Warmth, oral and epigastric burning, vomiting followed by abrupt onset of seizures
Imidazoline (*Visine*, *Afrin, clonidine*)			3–5 mL of 0.05% tetrahydrozoline (*Visine*) or 0.05% oxymetazoline (*Afrin*)	Potent central alpha agonists: central nervous system depression, inhibition of sympathetic output (miosis, bradycardia, hypotension, respiratory depression)
Phenothiazines: Chlorpromazine Thioridazine	25 15	200 mg	1–2 tablets	Anticholinergic symptoms, extrapyramidal effects (ataxia, rigidity, dystonia), CNS depression, seizures, arrhythmia
Methyl salicylate (*oil of wintergreen*)	200	1.4 g/mL	1/2 teaspoon	Hyperpnea, vomiting, tinnitus, fever, coma, seizure, acid-base and metabolic derangements
Theophylline	8.4	500 mg	1 tablet	Gastrointestinal effects, seizures, arrhythmias, hypokalemia, hyperglycemia, acidosis
Ammonium fluoride (*Armor All Wheel Cleaner*, *Rust Bust'R*)	Dependent upon fluoride concentration		2–5 mL if 17% ammonium fluoride or bifluoride	Fluoride binds Ca^{++} and Mg^{++} causing tissue deposition and injury. Fluoride also inactivates many enzymatic pathways (i.e., acetylcholinesterase) Multisystem organ dysfunction (CNS, cardiac, pulmonary), hypocalcemia, hypomagnesemia, hyperkalemia, cholinergic symptoms
Buprenorphine	1	8 mg	1–2 tablets	CNS depression, hypopnea/apnea, pinpoint pupils
Acetonitrile (artificial nail remover)			1 teaspoon	Metabolism yields cyanide that causes cellular hypoxia, CNS and cardiovascular dysfunction, severe lactic acidosis

46.3 Approach to the Child with the Unknown Ingestion

46.3.1 History

Historical data should be focused and obtained quickly. This should include the patient's past medical history, allergies, current medications, last meal, and events surrounding the ingestion. An accounting of all medications and other potential exposures such as cleaning substances in the home should be done. The history of ingestion of certain compounds (e.g., tricyclic antidepressants, cardiac medications) should prompt immediate concern due to the high likelihood of toxicity. Timing, route, possibility of co-ingestion, initial symptoms, and prehospital attempts at decontamination should be documented.

46.3.2 Physical Examination

Following a toxic ingestion, children may be asymptomatic or present with life-threatening symptoms including respiratory arrest, coma, seizures, arrhythmias, or hemodynamic instability. Children who are initially asymptomatic may develop symptoms later if absorption is impaired or a sustained release substance has been ingested. The clinician should be aware of signs and symptoms that comprise a toxidrome, a constellation of findings that characterize a specific ingestion. Common toxidromes are listed in Table 46.2.

A toxidrome is a constellation of findings that characterize a specific ingestion.

Bradycardia and hypotension are the most serious presenting features of an overdose and require immediate attention. Examples of drug classes that can present with **bradycardia** and **hypotension** include:

Central α_2-adrenergic receptor agonists: clonidine, guanfacine, oxymetazoline, tetrahydrozoline

β-Adrenergic receptor antagonists: propranolol, metoprolol, atenolol, carvedilol

Calcium channel blockers: diltiazem, verapamil, amlodipine, isradipine, nifedipine

Cardiac glycosides: digoxin, oleander (*Nerium oleander*), yellow oleander (*Thevetia peruviana*), foxglove, lily of the valley (*Convallaria majalis*), red squill (*Urginea maritima*)

Acetylcholinesterase inhibitors: organophosphates, carbamates, neostigmine, sarin

46.3.3 Laboratory Evaluation

The initial evaluation should be rapid and focused. Studies evaluating comprehensive toxicology screening in pediatric patients have concluded that these tests are costly and do not affect the management of most patients with a toxic ingestion. A reasonable approach to the child with an unknown ingestion includes:

1. *Blood glucose determination*. The rapid identification and treatment of toxin-induced hypoglycemia is crucial. Medications causing hypoglycemia include insulin, ethanol, salicylates, β-blockers, and sulfonylureas.
2. *Pulse oximetry and hemoglobin co-oximetry*. A blood gas with co-oximetry analysis can identify hypoxemia, hypercarbia, acid-base disturbances, and hemoglobinopathies (e.g., methemoglobin).

Serum chemistries may provide useful information regarding an ingestion. Anion gap and osmolar gap can be calculated and help determine the cause of an unknown ingestion.

Comprehensive qualitative toxicology panels often do not change the medical management of the poisoned patient.

Table 46.2 Common toxidromes

Toxidrome	Presentation	Pupils/vital signs	Causative agents
Anticholinergics ("blind as a bat, dry as a bone, red as a beet, hot as hades and mad as a hatter")	Mydriasis, dry flushed skin, fever, delirium, urinary retention, decreased bowel sounds, seizures	Mydriasis Tachycardia Hyperthermia Hypertension Tachypnea	Antihistamines Tricyclic antidepressants Scopolamine, atropine Benztropine Jimson weed, angel's trumpet
Cholinergics ("dumbbells")	Defecation, diarrhea, diaphoresis, urination, miosis, muscle weakness and fasciculations, bronchorrhea, emesis, lethargy, lacrimation, salivation, seizures	Miosis Bradycardia Hypothermia Tachypnea Hypotension	Organophosphates Carbamates Mushrooms
Hallucinogenics	Disorientation, hallucinations, anxiety, moist skin, seizures	Tachycardia Tachypnea Hypertension	LSD Mescaline Phencyclidine *Salvia divinorum*
Narcotics	Altered mental status, obtundation, hypoventilation, hypotension	Miosis Bradypnea Bradycardia Hypothermia Hypotension	Opioids Dextromethorphan
Sedative/hypnotics	Coma, confusion, sedation, ataxia, progressive CNS deterioration, hyporeflexia	Bradypnea Hypothermia Hypotension Bradycardia	Barbiturates Benzodiazepines Ethanol Anticonvulsants
Sympathomimetics	Delusions, paranoia, anxiety, diaphoresis, piloerection, hyperreflexia, seizures	Mydriasis Tachycardia Hypertension Hyperthermia Tachypnea	Cocaine Amphetamine Methamphetamine Phenylpropanolamine Ephedrine Albuterol
Salicylates	Tinnitus, confusion, agitation, coma, seizure, flushing, emesis	Hyperpnea Tachypnea Hyperthermia	Acetylsalicylic acid (ASA) Oil of wintergreen
Serotonin agonists	*Acute ingestion*: Restlessness, hallucinations, nausea, dizziness, blurred vision *Serotonin syndrome*: Altered mental status, myoclonus, rigidity, tremors, fever, hyperreflexia, autonomic instability, ataxia, seizures	Mydriasis Hyperthermia Tachycardia	Selective serotonin reuptake inhibitors (SSRIs) MAO inhibitors Lithium

3. *Electrocardiogram* (*ECG*). Dysrhythmias can occur as a result of a variety of poisonings. It is essential that arrhythmias be identified and treated early in the presentation of a child with a suspected toxic ingestion. Agents that are highly arrhythmogenic are summarized in Table 46.3.
4. *Serum chemistry*. A basic chemistry panel may provide information regarding an unknown toxin exposure. Calculation of an anion gap detects the presence of unmeasured anions that lead to severe acidosis. A normal anion gap is usually 8–12 and is estimated by the equation: $(Na^+) - (Cl^- + HCO_3^-)$. The mnemonic *MUDPILES CAT* is a useful mnemonic to remember common causes of an increased anion gap acidosis. The causes include methanol, metformin, uremia, diabetic ketoacidosis, paraldehyde, isoniazid and iron, lactate, ethylene glycol, salicylates, cyanide, alcohols (except isopropyl), theophylline, and toluene.
5. *Osmolar gap*. The calculated osmolality can be determined with the equation: $2(Na^+)$ + BUN/2.8 + glucose/18 + ethanol/4.6. An osmolar gap is calculated by subtracting the calculated osmolality from the measured osmolality. A normal gap is less than 10 mOsm. An elevated osmolar gap exists when unmeasured osmotically active molecules are present. Unmeasured osmotically active molecules that increase the osmolar gap include ketones and alcohols (methanol, ethanol, ethylene glycol, and isopropyl alcohol). Isopropyl alcohol is the only alcohol to create an osmolar gap but not an anion gap. In many institutions, quantitative assays for toxic alcohols are available allowing for detection of specific toxic alcohols.
6. *Quantitative drug assay.* Quantifying serum drug levels may have a significant impact on management of the poisoned child. Medications that can be quantified include aspirin, acetaminophen, antiepileptics, digoxin, alcohols, iron, lithium, methemoglobin, and theophylline. Use of comprehensive qualitative toxicology panels has been shown to be costly, and the results often do not change the clinical management of the poisoned child.

The HOBBIES mnemonic can be helpful in determining substances that can cause profound hypoglycemia in a small child: Hypoglycemics (sulfonylureas, metformin) Other (quinine), Beta-Blockers, Insulin, Ethanol, Salicylates

Table 46.3 Ingestions with the potential of causing arrhythmias

Ingestion	Arrhythmias
Tricyclic antidepressants	Sinus tachycardia, supraventricular tachycardia, wide QRS, prolonged QT, ventricular tachycardia, and fibrillation
Anticholinergics (i.e., diphenhydramine, Jimson weed)	Sinus tachycardia, QRS and QTc prolongation
Cholinergics (i.e., organophosphates, carbamates)	Bradycardia, atrioventricular block, and QTc prolongation
Ethylene glycol	Narrow or prolonged QRS and QT, ventricular tachycardia, and fibrillation
β-Blockers	Bradycardia, atrioventricular block, ventricular tachycardia, and fibrillation
Calcium channel blockers	Bradycardia, atrioventricular block, ventricular tachycardia, and fibrillation
Digitalis	Bradycardia, atrioventricular block, premature ventricular complexes, bigeminy, trigeminy, junctional tachycardia, ventricular tachycardia
Sympathomimetics (i.e., amphetamine, ephedrine, cocaine, MDMA)	Sinus tachycardia, supraventricular tachycardia, ventricular tachycardia

7. *Drugs of abuse.* Illicit drug assays should be ordered only when clinically indicated. False-positive results may occur. Over-the-counter cold remedies may result in false-positive tests for phencyclidine (PCP) and amphetamines, and the ingestion of poppy seeds can result in positive screening for opioids.
8. *Urinalysis.* Examination of the urine at times may be helpful in determining an unknown toxin. Calcium oxalate crystals may be visualized in the urine after ethylene glycol ingestion. Blood present on a urine dipstick but not visualized directly on a formal urinalysis may indicate myoglobinuria seen with rhabdomyolysis.
9. *Creatine phosphokinase (CPK).* CPK levels should be checked for patients that exhibit significant levels of psychomotor agitation to evaluate for associated rhabdomyolysis.
10. *Pregnancy.* A urine or serum pregnancy test should be ordered in women of childbearing age as the toxin may have direct and severe consequences to the unborn child.
11. *CT imaging of the brain.* Patients with altered mental status often require imaging of the brain to rule out concomitant trauma or unsuspected primary CNS pathology.

46.4 Stabilization

» *Treat the patient, not the poison.*

Stabilization of physiologic functions takes priority over the diagnosis of the specific toxin. Often, supportive measures are sufficient, and no specific therapy is required. Supportive measures include the evaluation and treatment of cardiopulmonary, neurologic, and metabolic abnormalities.

The adequacy of the airway and breathing should be addressed immediately. Supplemental oxygen should be administered for any degree of hypoxemia. Endotracheal intubation and mechanical ventilation should be considered in any child with progressive neurologic deterioration especially if gastric decontamination is required. Circulation must be maintained to ensure adequate organ perfusion, and any arrhythmias should be treated promptly. A rapid bedside glucose determination should be done upon presentation.

Stabilization of the poisoned patient takes priority over diagnosis of the specific toxin ingested.

The early use of naloxone in a suspected opioid overdose may prevent more invasive measures. Flumazenil (benzodiazepine antagonist) should not be given routinely as it may precipitate seizures if tricyclic antidepressants have been ingested or if benzodiazepines have been taken on a chronic basis. Consultation with poison control centers for assistance in monitoring and treating the poisoned patient should be considered.

The maintenance of the "ABCDs" (airway, breathing, circulation, disability/dextrose) are the most important initial therapies that must occur with all poisoned patients.

46.5 Decontamination and Prevention of Absorption

Many toxins are rapidly absorbed from the gastrointestinal tract, skin, and respiratory system. The development of severe toxicity may be avoided if further absorption can be prevented. Dermal decontamination consists of flushing the skin with tepid water and removal of all exposed clothing. Ocular decontamination is also performed by copious irrigation of the eyes with an isotonic saline solution, often via a Morgan Lens, until the eye is adequately rinsed and the pH has normalized. Healthcare professionals should wear protective clothing and eyewear if transdermal or transocular transmission is a risk before, during, or after formal decontamination.

Healthcare workers should wear protective clothing if the possibility of transdermal transmission exists.

The American Academy of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists have reviewed multiple decontamination and enhanced elimination strategies. Current recommendations for the use of each decontamination strategy are given below.

46.5.1 Ipecac

The emetogenic medication ipecac is not recommended for use due to its limited effectiveness and potential for morbidity.

46.5.2 Activated Charcoal

Charcoal acts to minimize toxicity through physical adsorption of enteral toxins directly onto its large surface area, thus preventing systemic absorption. Poisons not adsorbed by activated charcoal (AC) include metals, strong acids and bases, alcohols, cyanide, and hydrocarbons. AC may reduce systemic absorption of certain ingested substances by 40–50% if given within the first hour after ingestion. Use of AC is contraindicated in patients that have or are anticipated to develop an impaired ability to protect their airway because aspiration results in pneumonitis. Other complications include bowel obstruction and perforation. Because of these limitations, and limited evidence that AC improves clinical outcomes, routine use is not recommended. Single-dose AC may be considered in patients who have ingested a potentially toxic amount of a poison (which is known to be adsorbed to charcoal) up to 1 h prior to presentation. When indicated, an initial 1–2 g/kg dose is recommended.

46.5.3 Multiple-Dose Activated Charcoal

Multiple-dose activated charcoal (MDAC) shares a similar adsorption mechanism to single-dose activated charcoal but theoretically provides additional benefit by enhancing elimination of toxins that undergo extensive enterohepatic circulation. MDAC has been shown to increase drug elimination in life-threatening overdoses of dapsone, phenobarbital, carbamazepine, quinine, or theophylline. MDAC has not consistently demonstrated a reduction in morbidity and mortality in adult studies. It should be used with caution and under the guidance of a toxicologist.

46.5.4 Cathartics

Cathartics, including sorbitol, magnesium sulfate, and magnesium citrate, are used with the intention to decrease the absorption of substances by accelerating the expulsion of a substance from the gastrointestinal tract. Cathartic use is not recommended because of a lack of evidence for benefit and evidence for harm in children, including electrolyte and fluid imbalances.

46.5.5 Gastric Lavage

Gastric lavage is performed with the intention of decreasing the systemic absorption of toxins by mechanically removing toxins from the stomach. It requires assurance of airway protection and placement of a gastric tube.

Lavage is performed within 30 min of ingestion by instilling and then withdrawing normal saline aliquots of 50–100 mL in children and 150–200 mL in adolescents until the fluid is clear. Gastric lavage may be useful in only rare cases in which there has been a very recent ingestion (30 min to 1 h) of a life-threatening toxicant that is not rapidly absorbed and not effectively adsorbed by AC. It is absolutely contraindicated without a protected airway and in ingestions involving caustics or hydrocarbons. Current guidelines recommend against using the routine use of gastric lavage.

46.5.6 Whole Bowel Irrigation (WBI)

This technique of decontamination consists of intestinal irrigation with large volumes of polyethylene glycol electrolyte solution. Recommended dosing is 500 mL/h in toddlers and 1–2 L/h in adolescents. Whole bowel irrigation can be considered for potentially toxic ingestions of metals (i.e., iron, lead) and illicit drug packets. It may also be considered for potentially toxic ingestions of sustained-release or enteric-coated medications, particularly in patients presenting later than 2 h with ingestions not amenable to AC (iron tablets, lead containing foreign bodies).

46.5.7 Enhanced Excretion and Forced Diuresis

Increasing urine volume with diuretics does not increase the renal excretion of toxins. Inappropriate use of diuretics may be harmful as they may lead to volume depletion and metabolic derangements. Other therapies to increase excretion of the toxin or remove it directly from the serum are discussed below briefly.

46.5.8 Urine Alkalinization

Alkalinizing urine promotes the renal excretion of weakly acidic drugs by increasing the proportion of ionized (charged) drug in the renal tubule, otherwise known as ion trapping. Charged particles diffuse poorly from the renal tubular lumen back to systemic circulation. This allows "trapped ions" to be eliminated through urinary output. Toxins for which alkalinization is appropriate need to be predominantly eliminated by the kidneys, be distributed in the extracellular compartment, be weak acids, and have low protein binding.

Alkalinization can be accomplished with the addition of 50–75 meq/L of bicarbonate to maintenance fluids and aiming for a urine pH greater than 7.5.

Urine alkalinization is considered the first-line treatment for moderate salicylate poisoning that does not meet criteria for hemodialysis. Other possible toxicologic indications for urinary alkalinization include exposures to chlorpropamide, chlorophenoxy herbicides, methotrexate, phenobarbital, diflunisal, and 2,4-dichlorophenoxyacetic acid.

Ion trapping enhances the excretion of weakly acidic drugs by increasing the pH of the urine. Toxins for which alkalinization is appropriate need to be predominantly renally eliminated, be distributed in the extracellular compartment, be weak acids, and be minimally protein-bound.

46.5.9 Extracorporeal Techniques

Hemodialysis can effectively remove several toxins from the patient's circulation and correct fluid and electrolyte imbalances.

Hemodialysis (HD) can quickly correct fluid, electrolyte, and acid-base disturbances in the poisoned patient and can be an effective mode of elimination of certain poisons. To be easily removed by hemodialysis, the toxin must have:

- Low molecular weight (optimally less than 5000 Da)
- Low protein binding

- Low volume of distribution
- Low endogenous clearance
- High water solubility

A hemodialysis circuit cannot remove poisons that are very large or highly protein-bound. However, because protein binding sites may be saturated in an overdose, a larger portion of unbound poison may be present and amendable to HD (e.g., valproic acid). HD has added value of rapidly correcting electrolyte and acid-base disturbances. Toxins readily removed by hemodialysis include alcohols, salicylates, lithium, phenobarbital, and procainamide.

Continuous venovenous hemodialysis (CVVHD) or hemodiafiltration (CVVHDF) can be used for toxin removal if hemodynamic compromise exists. CVVHDF removes toxins slower than HD due to lower blood flow rates and filtration. CVVHDF may also provide better filtration of larger molecules as the filter allows much larger molecules up to 40,000 Da to pass through as opposed to the small pore filter of conventional hemodialysis.

Hemoperfusion is the use of hemodialysis with a cartridge containing an adsorbent material.

Hemoperfusion substitutes the dialysis membrane used in conventional hemodialysis with a cartridge containing an adsorbent material (carbon or charcoal). Blood is passed through the cartridge, and toxins with a high affinity for the filter are adsorbed. This allows larger molecules with high protein binding and low water solubility to be eliminated. Hemoperfusion has been used successfully in overdoses of theophylline, salicylates, and carbamazepine. However, hemoperfusion is associated with greater complications (hypocalcemia, thrombocytopenia, leucopenia, hypoglycemia) than HD and should be used with caution.

46.5.10 Intravenous Lipid Emulsion Therapy

ILE therapy involves the intravenous infusion of a large amount of lipids to facilitate the treatment of fat-soluble drug toxicity. The proposed mechanism is described by the "lipid sink theory." Lipophilic substances are drawn into the "lipid sink" created by infusing exogenous lipid. A concentration gradient develops causing the lipophilic toxin to move away from sensitive tissues (the myocardium or brain) and into the vascular "lipid sink." The toxin is removed from vulnerable tissue and is concentrated into the vascular space where it can be more easily eliminated.

Intralipid therapy can be considered in the treatment of severe toxicities due to lipophilic drugs, especially those given parenterally (local anesthetics).

ILE therapy was introduced as a treatment for acute local anesthetic toxicity (e.g., bupivacaine). ILE is likely to be more useful in parenteral overdoses; however, its use has been described in refractory cardiac toxicity associated with enteral lipophilic drugs. These include verapamil, beta-blockers, tricyclic antidepressants, chlorpromazine, and antidysrhythmics (e.g., flecainide). Despite the paucity of evidence supporting routine use of ILE therapy, it may be an option for critically ill patients who remain unstable despite standard therapeutic measures. The dosing protocol consists of an IV bolus of 1–1.5 mL/kg given over 1 min of a 20 percent lipid emulsion solution. ILE therapy should be guided by a medical toxicologist or poison control center.

46.6 Antidotes

Antidotes can be competitive or physiological antagonists that alter a toxin's absorption, metabolism, or excretion. Specific antidotes are summarized in Table 46.4.

Table 46.4 Common ingestions and antidotes

Ingestion	Antidote	Mechanism	Dose	Side effects of antidote
Acetaminophen	*N*-Acetylcysteine	Serves as precursor for glutathione synthesis and limits production of NAPQI	140 mg/kg loading dose followed by 70 mg/kg every 4 h for 17 doses or until normalization of liver function	Nausea, emesis
Anticholinergics (i.e., antihistamines, atropine)	Physostigmine	Acetylcholinesterase inhibitor which acts to increase acetylcholine levels	0.02 mg/kg	Bradycardia, asystole, bronchospasm
				Contraindicated with multi-ingestions
β-Blockers and calcium channel blockers	Glucagon	Counters insulin effects and possesses inotropic and chronotropic activity	0.05–0.15 mg/kg initially and continuous infusion 0.05–0.1 mg/kg/h	Hyperglycemia
Benzodiazepines	Flumazenil	Competitive antagonist at benzodiazepine receptor	0.3 mg every 1 min to max dose of 3 mg	May precipitate seizures in patients using chronic benzodiazepine
Digoxin	Digoxin-specific antibody (Fab) fragments	Binds free digoxin	Dose of digoxin-specific Fab antibody determined in conjunction with toxicologist	Severe hypokalemia, allergic reaction
Ethylene glycol	Ethanol	Ethanol and fomepizole are competitive inhibitors of alcohol dehydrogenase that prevent production of toxic metabolites	Ethanol:	Sedation, emesis, hypoglycemia
			750 mg/kg initial dose followed by infusion 80–150 mg/kg/h	
			Goal level = 100 mg/dL	
	Fomepizole	Pyridoxine and thiamine divert ethylene glycol metabolism to nontoxic metabolites	Fomepizole: 15 mg/kg initially and then 10–15 mg/kg q 12 h until level < 20 mg/dL dose every 4 h if	
			Patient is being dialyzed	
	Pyridoxine (vitamin B_6)		Pyridoxine: 10–50 mg/24 h	
	Thiamine (vitamin B_1)		Thiamine:10–50 mg/24 h	
Methanol	Ethanol	As above	As above	As above
	Fomepizole	As above	As above	
Narcotics (i.e., morphine)	Naloxone	Opioid antagonist	0.01–0.1 mg/kg initially, may require continuous infusion	Nausea, emesis, diaphoresis, diarrhea (withdrawal symptoms) if patient is addicted to narcotics
Organophosphates and carbamates	Atropine	Muscarinic receptor blocker	0.05 mg/kg every 5–10 min, infusions of 0.02–0.08 mg/kg/h may be required	Tachycardia, anticholinergic effects

Table 46.4 (continued)

Ingestion	Antidote	Mechanism	Dose	Side effects of antidote
Organophosphates	Pralidoxime	Competes with phosphate moiety for organophosphate-acetylcholinesterase complex and causes release of acetylcholinesterase	25–50 mg/kg initially followed by infusion 5–10 mg/kg/h	Nausea, tachycardia, bronchospasm
Sulfonylureas (glipizide, glyburide, glimepiride)	Octreotide	Synthetic peptide analogue of somatostatin and causes inhibition of insulin secretion	4–5 ug/kg/day SC divided every 6 h up to the adult dose of 50 ug every 6 h	Nausea, abdominal cramping, diarrhea, pain at injection site
Isoniazid (INH)	Pyridoxine	Overcomes impaired GABA synthesis caused by INH inhibition of pyridoxine phosphokinase	1 g of pyridoxine for each gram of INH ingested or 70 mg/kg in a child. Max dose of 5 g	Minimal side effects at therapeutic doses. At supratherapeutic doses can cause sensory neuropathies, ataxia

46.7 Selected Overdoses of Importance to the Pediatric Intensivist

46.7.1 Acetaminophen

Acetaminophen (N-acetyl-p-aminophenol; APAP) is among the most commonly overdosed pharmaceuticals. It is rapidly absorbed from the GI tract with complete absorption generally occurring within 4 h. Doses greater than 150–200 mg/kg have been associated with toxicity in children.

Under normal conditions, 80–90% of APAP undergoes sulfation and glucuronidation to produce nontoxic conjugates. Approximately 5% of APAP is metabolized via hepatic cytochrome P_{450} enzymes to N-acetyl-*p*-benzoquinone imine (NAPQI). NAPQI must be conjugated with glutathione to prevent hepatocellular toxicity (Fig. 46.1). In overdoses, a greater amount of APAP undergoes cytochrome metabolism causing glutathione depletion. When glutathione levels are depleted to less than 70% of normal, NAPQI accumulates and binds to hepatocyte macromolecules. Binding to hepatocellular macromolecules produces hepatocellular damage usually in a central lobular distribution.

Clinical manifestations of acute acetaminophen overdose can be divided into four stages. In the first 24 h post ingestion (stage I), patients may exhibit anorexia, pallor, nausea, and vomiting but appear normal otherwise. Elevated serum acetaminophen levels are common, but biochemical evidence of hepatic injury is rare, even in children who will ultimately develop hepatotoxicity.

Stage II occurs during the next 24–72 h and is heralded by right upper quadrant pain and elevations in liver enzymes, prothrombin time (PT), and bilirubin. Aspartate aminotransferase (AST) is the most sensitive measure of hepatotoxicity in this phase. Subsequent hepatic failure occurs in only a small fraction of patients with initial hepatic dysfunction.

Stage III occurs 72–96 h after ingestion. Nausea and vomiting reappear, and patients may develop jaundice, myocardial dysfunction, hemorrhage, and renal failure. Severely toxic patients develop hepatic necrosis and encephalopathy. Laboratory values demonstrate AST and alanine transferase (ALT) values

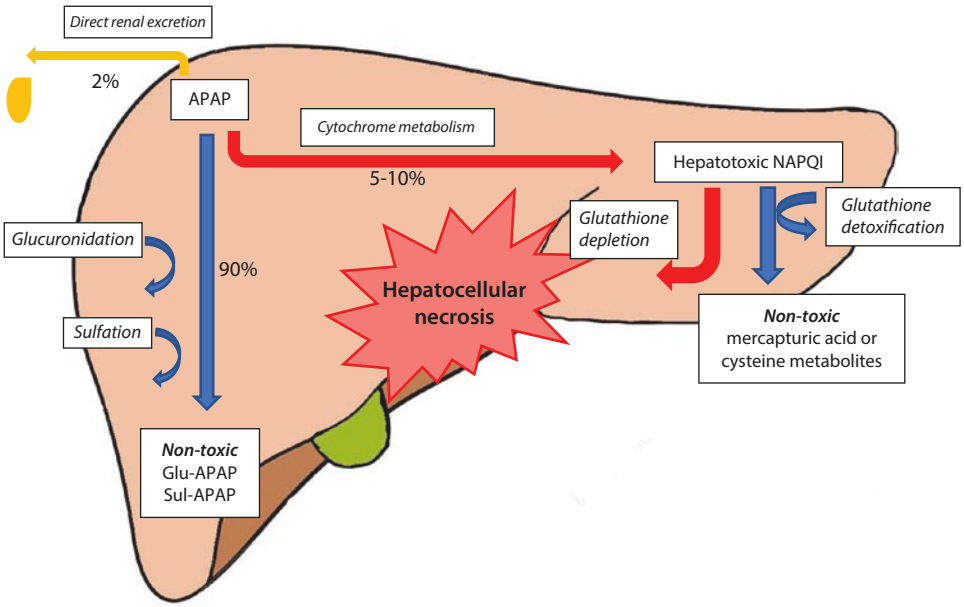

Fig. 46.1 APAP hepatic metabolism. Under normal conditions, 2% of APAP is excreted unchanged in the urine, 80–90% of APAP undergoes sulfation and glucuronidation to produce nontoxic conjugates, and approximately 5% of APAP is metabolized via hepatic cytochrome P450 enzymes to N-acetyl-p-benzoquinone imine (NAPQI). NAPQI must be conjugated with glutathione to produce nontoxic mercapturic acid or cysteine metabolites, thereby preventing hepatocellular toxicity. Courtesy FA Maffei, edited by A. Czworniak

Glutathione levels are depleted in acetaminophen overdose leading to NAPQI binding to hepatocytes and hepatocellular damage.

A rising PT, elevated creatinine, metabolic acidosis, and encephalopathy are associated with a high morbidity and mortality in acetaminophen overdose.

The most common cause of mortality in acetaminophen overdose is cerebral edema.

above 10,000 IU/L. Elevations of PT (INR) and bilirubin with development of hypoglycemia and metabolic acidosis may occur and are important prognostic indicators.

Stage IV occurs between 4 days and 2 weeks post ingestion. If damage occurring in stage III is reversible, resolution of the hepatic dysfunction occurs, and laboratory values normalize by 5–7 days after ingestion. If irreversible liver damage has occurred, hepatic failure ensues, and transplantation is required for survival.

Renal dysfunction may occur in over 25% of those with significant hepatotoxicity and is more common after chronic toxic exposure. Myocardial and pancreatic dysfunction may be concomitant with hepatic toxicity, but never occur as isolated organ damage. The most common cause of mortality is cerebral edema associated with hepatic encephalopathy.

Supportive care and N-acetylcysteine (NAC) therapy are proven therapies for acetaminophen toxicity. For acute ingestions, activated charcoal administration decreases the number of patients in the "probable" or "possible toxicity" areas of the nomogram if delivered within the first 2–4 h after a potentially toxic acute ingestion. Measurement of plasma acetaminophen level should be done 4 or more hours after a suspected ingestion. To determine if NAC therapy is required, the acetaminophen level should be plotted on the Rumack-Matthew nomogram (Fig. 46.2). The nomogram is only valid for acute ingestions with known time of ingestion. The risk of hepatotoxicity from chronic acetaminophen overdose or an overdose with concurrent alcohol use may be underestimated using the nomogram.

NAC serves as a precursor for glutathione synthesis and acts to limit the formation of the potentially toxic NAPQI and detoxifies NAPQI that has already formed. Children falling into the possible or probable hepatic toxicity areas of the Rumack-Matthew nomogram should be started on NAC. It is nearly 100% effective in preventing mortality and reversing hepato toxicity from acute acetaminophen overdoses if administered within 8 h of the ingestion, and its use may be beneficial up to 36 h after the ingestion. NAC may be administered orally or intravenously with similar efficacies if given within the first 8–24 h after an acute ingestion.

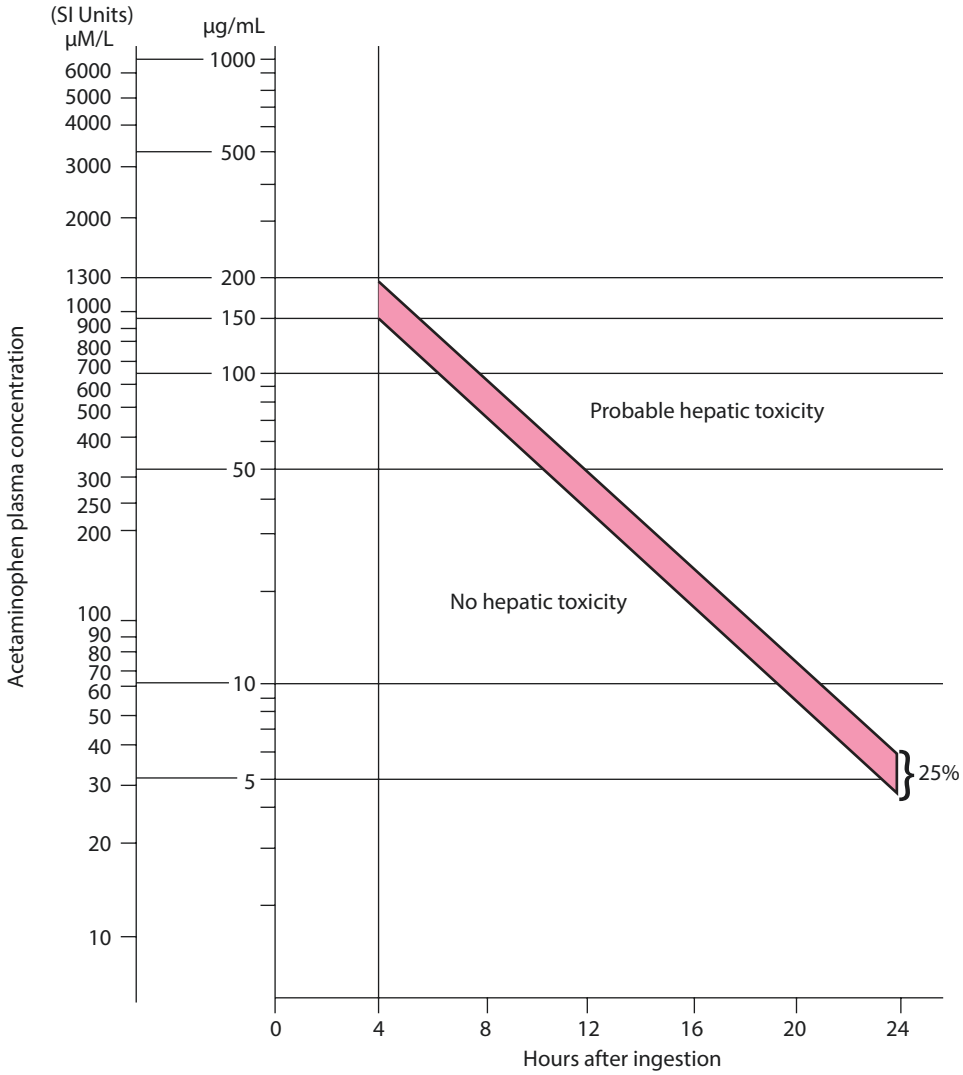

Fig. 46.2 Rumack-Matthew nomogram

Intravenous NAC is associated with anaphylactoid reactions in approximately 15% of patients with severe reactions occurring in <1% of patients. Patients with a history of asthma may be predisposed to NAC-induced allergic reactions, and close monitoring is required during treatment. If hepatic dysfunction and/or persistent emesis is present, intravenous NAC is preferred. IV NAC is given as a 150 mg/kg load (with a maximum dose of 15 g) over 1 h followed by a second 50 mg/kg (maximum 5 g) dose infused over 4 h followed by a 100 mg/kg (maximum 10 g) dose infused over 16 h. This 21 hour dosing regimen is shorter than the 72 hour oral regimen. Oral NAC has a potent "rotten eggs" odor and taste and may cause emesis. Oral NAC is administered as a loading dose of 140 mg/kg and continued at a dose of 70 mg/kg every 4 hours for 17 doses. Charcoal administration at the time of presentation does not preclude the use of oral NAC.

Patients with a history of an indolent ingestion may not meet Rumack-Matthew criteria for NAC therapy. Patients with any detectable acetaminophen levels and elevated transaminases warrant NAC treatment, whereas patients with undetectable acetaminophen levels and normal transaminases do not require NAC treatment. The use of NAC in patients with a history of acetaminophen overdose who have undetectable APAP and elevated transaminases

Persistent acidosis, worsening synthetic function, and/or progressive encephalopathy despite NAC therapy should prompt referral to a transplant center.

is less clear. Consultation with a medical toxicologist is recommended in these rare cases.

The incidence of APAP-induced ALF is low. Less than 10% of patients presenting with hepatotoxicity will require liver transplantation. However, the intensivist should prepare for the possibility of ALF during stage III. Clinical scores such as the King's College Criteria (KCC) have been used to predict the need for liver transplantation in adults but are not validated in children. In adults, the KCC were developed to determine which patients with ALF should be listed for liver transplant. The presence of one of the following physiologic derangements, which include those described in the KCC, should prompt a consultation and/or transfer to a liver transplantation center:

The "150 rule" for acetaminophen toxicity: The toxic dose is 150 mg/kg. Give NAC if level is > 150 mcg/mL 4 hours post ingestion. The initial loading dose of NAC is 150 mg/kg IV (140 mg/kg PO).

- Acidosis (admission arterial pH < 7.30)
- Hepatic encephalopathy (grade III or IV), and coagulopathy (PT > 100 s), and acute kidney injury (creatinine >3.4 mg/dL)
- Hyperlactatemia (4 hour lactate >3.5 mmol/L, or 12 hour lactate >3.0 mmol/L)
- Hyperphosphatemia (phosphate >3.7 mg/dL at >48 hours post ingestion)

46.7.2 Salicylates

The incidence of salicylate poisonings in children has declined due to the use of alternative antipyretics. Common medications containing salicylates are aspirin, oil of wintergreen, and Pepto-Bismol. In therapeutic doses, salicylates inhibit cyclooxygenases, block prostaglandin production, and have antithrombotic effects by inhibiting platelet generation of thromboxane A2. They produce anti-inflammatory, analgesic, and antipyretic effects.

Salicylates interfere with cellular metabolism by uncoupling oxidative phosphorylation leading to acidosis, heat production, and hypoglycemia.

The pathophysiology of salicylism is multifactorial. Salicylates are weak acids that interfere with the Krebs cycle and uncouple oxidative phosphorylation. This limits the production of ATP and leads to accumulation of pyruvic and lactic acids. Uncoupled oxidative phosphorylation in the mitochondria also results in heat generation and increased body temperature. Salicylates induce fatty acid metabolism resulting in ketone formation, which further adds to the anion gap metabolic acidosis. Lastly, disruption of the respiratory chain impairs oxygen uptake at the cellular level despite the maintenance of oxygen delivery.

Acute ingestion causes nausea and vomiting due to gastric irritation. Mild tachypnea and tinnitus are early findings. Hyperpnea and hyperventilation are due to direct stimulation of the medullary respiratory center. Central nervous system abnormalities such as agitation, confusion, seizures, restlessness, and coma suggest severe toxicity. Hyperpyrexia and hemodynamic collapse may ensue. Non-cardiogenic pulmonary edema and acute respiratory distress syndrome can occur due to disruption of the alveolar endothelial barrier.

Laboratory abnormalities are numerous but are often nonspecific. Respiratory alkalosis with a concomitant anion gap metabolic acidosis occurs early, whereas respiratory acidosis is a late finding. Multiple electrolyte and metabolic derangements may occur and include hypokalemia, hyperglycemia, hypoglycemia, rhabdomyolysis, and elevation of liver enzymes.

Tachypnea and respiratory alkalosis occur early, whereas hyperthermia and respiratory acidosis are late findings that are consistent with severe salicylate toxicity.

Acute ingestions of 150–300 mg/kg of salicylates are associated with mild symptoms and greater than 500 mg/kg with severe symptoms and death. Marked hyperthermia and respiratory acidosis are indications of severe poisoning.

Serum salicylate levels should be obtained in patients with a history of significant ingestion or signs and symptoms consistent with toxicity. Therapeutic goals include supportive care (e.g., ABCDs, correction of electrolyte abnormalities), decontamination, and enhancing salicylate excretion. Hypoglycemia

and hypokalemia may require correction. The use of activated charcoal has been found to be beneficial in salicylate poisoning if given early after the ingestion. Each gram of charcoal adsorbs 550 mg of salicylic acid. A dose of 1 g/kg with maximum single dose of 50 g is recommended.

Alkalinization of the urine can increase salicylate excretion through "ion trapping" as previously discussed. Maintaining urine pH greater than 7.5 is recommended for ingestions with salicylate levels greater than 30 mg/dL. Attention to the adequacy of urine output (1–2 mL/kg/h) and maintenance of normal serum electrolytes during alkalinization is essential. Typically, alkalinization is begun using an intravenous sodium bicarbonate bolus of 1–2 mEq/kg, followed by a continuous infusion of sodium bicarbonate at approximately 1.5–2 times maintenance requirements. For life-threatening symptoms (e.g., pulmonary edema, intractable acidosis, coma) or when levels exceed 100 mg/dL, hemodialysis should be instituted. Hemoperfusion may be superior to hemodialysis if a co-ingestion amenable to filter adsorption has also occurred.

46.7.3 Tricyclic Antidepressants (TCAs)

Children are at significant risk for TCA toxicity due to their narrow therapeutic window. One to two pills in children can cause serious morbidity and mortality. Doses of merely 10–20 mg/kg of TCAs can be toxic and life-threatening; therefore, the child with suspected ingestion requires immediate evaluation and rapid initiation of therapy if warranted.

TCAs have a large volume of distribution and are rapidly absorbed. The pathophysiology of TCA toxicity is complex and can result in life-threatening cardiovascular changes. The pharmacologic properties responsible for the clinical manifestations of toxicity include:

(i) Muscarinic acetylcholine receptor blockade resulting in anticholinergic effects that characterize the early stages of intoxication. These may include CNS abnormalities such as agitation or depression of consciousness.
(ii) Inhibition of CNS and peripheral neurotransmitter (e.g., norepinephrine, serotonin) reuptake. Of note, the initial blocking of norepinephrine reuptake may lead to a transient hyperadrenergic state that is followed by eventual catecholamine depletion.
(iii) Alpha-adrenergic receptor blockade causing peripheral vasodilatation and subsequent hypotension.
(iv) Slowing of sodium flux through fast channels of the myocardium causing an anesthetic effect on the myocardium (quinidine-like effect). Slowing of phase 0 depolarization of the action potential in the His-Purkinje system and ventricles results in prolongation of ECG intervals and ultimately arrhythmias.

Direct myocardial toxicity in combination with catecholamine depletion and alpha-adrenergic blockade may produce profound cardiovascular dysfunction. TCA overdoses present with cardiovascular and central nervous system alterations. Patients may have delirium, psychosis, lethargy, seizures, or coma. Anticholinergic signs of toxicity include fever, ileus, and urinary retention. Conduction delays such as QRS and QT prolongation can occur and may herald the onset of arrhythmias such as sinus tachycardia, supraventricular tachycardia, bradycardia, Torsades de pointes, ventricular fibrillation, and asystole. As TCAs can have devastating cardiovascular effects, the single most important test to guide therapy and prognosis remains the 12-lead surface ECG.

A 12-lead ECG should be obtained in all suspected TCA ingestions because the width of the QRS interval is the clinical feature most associated with severity of toxicity.

Important ECG changes include the following:

(i) Prolongation of the QRS complex: Blockage of fast sodium channels slows phase 0 depolarization of the action potential. Ventricular depolarization is delayed and leads to a prolonged QRS interval. Patients with QRS intervals longer than 100 ms are at risk for seizures, and patients with QRS intervals longer than 160 ms are at risk for arrhythmias. The QRS interval is best evaluated using the limb leads.

(ii) R wave in aVR greater than 3 mm: TCAs may have a greater selectivity and toxicity to the distal conduction system of the right side of the heart. The reason is unknown, but the effect can be observed as an exaggerated height of the R wave in aVR. Some data suggest that this finding may be more predictive of seizure and arrhythmia than prolongation of the QRS complex.

(iii) R/S ratio more than 0.7 in aVR.

(iv) QT interval prolongation.

(v) Sinus tachycardia: Usually secondary to peripheral anticholinergic effects.

(vi) Arrhythmias.

Qualitative screening for TCAs is rapidly available in most institutions. However, false positives due to cross-reactivity with other medications such as diphenhydramine, phenothiazines, cyclobenzaprine, and carbamazepine can occur. Quantitative levels of TCA are costly and not rapidly available and add little to the management of the patient with a TCA overdose.

Treatment should focus on stabilization of cardiopulmonary function by addressing the ABCDs and the rapid institution of sodium bicarbonate if cardiac toxicity is evident. Activated charcoal may be administered to decrease gastric absorption if given within 1 h after ingestion.

The most important therapy in TCA poisoning is alkalinization and sodium loading which have been shown to be effective in treating conduction disturbances and hypotension.

The cornerstone of therapy for tricyclic antidepressant-induced cardiotoxicity remains alkalinization and sodium loading. Sodium bicarbonate has been shown to be effective in the treatment of TCA-induced conduction disturbances, ventricular arrhythmias, and hypotension. Sodium bicarbonate attenuates TCA cardiotoxicity via several mechanisms. Alkalinization of blood to a pH of 7.45–7.55 appears to uncouple TCA from myocardial sodium channels. The additional sodium increases extracellular sodium concentration and improves the gradient across the channel. An initial dose of 1–2 mEq/kg of sodium bicarbonate followed by a continuous infusion can be utilized to maintain the serum pH approximately 7.5. Although the most commonly used infusion involves adding sodium bicarbonate 100–150 mEq to each liter of 5% dextrose, the resulting solution is slightly hypotonic or isotonic regarding its sodium content. Adding 100–150 mEq of sodium bicarbonate to 5% dextrose 0.45% sodium chloride produces a moderately hypertonic solution which may further decrease TCA cardiotoxicity. Therapy with 3% hypertonic saline should be considered in patients who are already alkalemic.

Hypotension should be treated with volume expansion and sodium bicarbonate as discussed above. If hypotension persists, a direct-acting catecholamine such as norepinephrine should be used to maintain mean arterial pressure. Seizures should be treated with benzodiazepines. Seizures requiring a long-acting anticonvulsant are best treated with phenobarbital. Phenytoin should be avoided due to its potential arrhythmogenic effects.

As discussed earlier, intravenous lipid emulsion infusion has been used in TCA toxicity unresponsive to standard therapy. There is a paucity of evidence other than case reports supporting its use. Lipid therapy should be guided by a medical toxicologist or poison control center. The dosing protocol consists of an IV bolus of 1–1.5 mL/kg given over 1 min of a 20 percent lipid emulsion solution. The dose can be repeated up to three times and followed by a 0.25 mL/kg infusion if cardiac instability persists.

46.7.4 Serotonergic and Non-serotonergic Antidepressants

Selective serotonergic reuptake inhibitors (SSRIs) are among the most commonly prescribed antidepressants in the United States because of their wide therapeutic index. Morbidity and mortality from overdose are far less frequent than observed with tricyclic antidepressants. The class includes fluoxetine, paroxetine, sertraline, citalopram, and escitalopram.

Large intentional overdoses can be associated with sedation, agitation, diaphoresis, tremors, hyperreflexia, clonus, tachycardia, hyperthermia, nausea, vomiting, flushing, seizures, coma, or other significant symptoms of toxicity. Serotonin syndrome is present when autonomic, neuromuscular, and mental status changes are present in the context of serotonergic toxicity. Serotonin syndrome rarely occurs after isolated SSRI ingestions and is more likely to manifest following a mixed serotonergic ingestion (e.g., monoamine oxidase inhibitor) or following a change in SSRI therapy (e.g., increase in dose or adding an additional agent). Serotonin syndrome caused by isolated SSRI ingestion tends not be severe. Formal diagnostic criteria include Sternbach's diagnostic criteria and the Hunter Toxicity Criteria.

Of the multiple SSRI medications, citalopram appears to have the greatest potential for cardiotoxicity. Citalopram has been associated with a variety of cardiac conduction disturbance including QRS widening, prolonged QTc, and ST segment changes especially with larger ingestions.

The mainstay of treatment for SSRI toxicity is supportive care. Wide QRS complex tachycardia can be treated in a similar fashion as TCA cardiotoxicity utilizing sodium bicarbonate boluses followed by a bicarbonate infusion. Benzodiazepines are effective therapy for agitation and seizures.

Serotonin syndrome may produce clonus, diaphoresis, muscular rigidity, and severe hyperthermia. It requires emergent treatment including attention to the ABCDs, IV hydration, sedation, and rapid cooling. Sedation with benzodiazepines may decrease agitation, rigidity, and autonomic instability. Progressive agitation, rigidity, and hyperthermia, despite benzodiazepines, require intubation and neuromuscular blockade. Antiserotonergic medications such cyproheptadine or chlorpromazine can be utilized although their efficacy is not clear. Cyproheptadine is available only as an enteral formulation and must be administered via a nasogastric or orogastric tube. Acetaminophen, NSAIDs, or aspirin are unlikely to control hyperthermia as the increased temperature is due to increased muscle activity.

Serotonin syndrome rarely occurs after isolated SSRI ingestions.

Serotonin syndrome is often confused with neuroleptic malignant syndrome (NMS) as both have rigidity, diaphoresis and hyperthermia as key features. ► Box 46.1 compares key features of the two syndromes.

Box 46.1 Distinguishing Features of Serotonin Syndrome and Neuroleptic Malignant Syndrome

Onset
- Serotonin syndrome develops over 24 h
- NMS develops over days to weeks

Pupils
- Pupils are usually dilated in serotonin syndrome
- Pupils are usually normal in NMS

Reflexes
- Serotonin syndrome is characterized by hyperreflexia and myoclonus
- NMS involves sluggish neuromuscular responses and bradyreflexia

Muscles
- Serotonin syndrome causes muscles to be rigid and hyperreactive (e.g. tremor, clonus)
- NMS characterized by "lead pipe rigidity"

Course
- Serotonin syndrome often resolves over 1–3 days
- NMS typically requires 7–10 days to completely resolve

46.7.5 Anticholinergics

Anticholinergics include atropine, diphenhydramine, scopolamine, cyclobenzaprine, Jimson weed, angel's trumpet, and benztropine. However, toxicity can occur with a wide variety of medications that have anticholinergic properties. These include TCAs, cough and cold preparations, and even illicit drugs.

Acetylcholine is the neurotransmitter at the muscarinic receptor within the central nervous system and parasympathetic nervous system. Toxicity occurs when the drug competitively binds the peripheral and central acetylcholine muscarinic receptors. This binding prevents neurotransmission via acetylcholine and thus inhibition of cholinergic actions (i.e., "anticholinergic").

Children with anticholinergic ingestion may present with hyperpyrexia, dry and flushed skin, dilated pupils, urinary retention, hypertension, and delirium.

The clinical symptoms of anticholinergic poisoning form a common toxidrome (Table 46.2) easily recalled by the mnemonic: "blind as a bat, dry as a bone, red as a beet, hot as hades, and mad as a hatter." Patients may present with dry and flushed skin, dilated pupils, tachycardia, hypertension, seizures, and urinary retention. Patients are often delirious and may demonstrate CNS stimulation or stupor.

Serum electrolytes should be obtained, and co-ingestions excluded since anticholinergic medications may be in a preparation with other drugs (e.g., acetaminophen with diphenhydramine). An ECG should be done to evaluate for QRS and QT prolongation. If QRS or QT prolongation is present, the child should be treated with sodium bicarbonate and sodium loading as with tricyclic antidepressant ingestions. Because anticholinergic medications impair gastric and intestinal motility, delayed and prolonged absorption can occur. Seizures and delirium should be treated with benzodiazepines and supportive care.

Physostigmine is a carbamate acetylcholinesterase inhibitor that binds reversibly to inhibit the enzyme acetylcholinesterase present in the neural synapses of both the peripheral and central nervous system (CNS). Physostigmine's acetylcholinesterase activity prevents the breakdown of acetylcholine and increases its concentration at muscarinic receptor. The increased concentration of acetylcholine overcomes the anticholinergic blockade.

There is controversy regarding the routine use of the anticholinesterase physostigmine. Reversal of the anticholinergic effects may result in the predominance of cholinergic effects and include bradycardia and bronchospasm.

Its use should be limited to patients with severe CNS toxicity and when coingestion of cardiotoxic drugs has been ruled out (e.g., TCAs). If available, a medical toxicologist should guide its use. Physostigmine is administered at a dose of 0.02 mg/kg IV (maximum 0.5 mg) given over 5 min. Repeated administration may be necessary owing to the 15-min half-life of physostigmine.

46.7.6 Muscle Relaxants

Due to their common availability, muscle relaxant overdoses have increased in frequency. Two common muscle relaxants that may have significant toxicity associated with overdoses are cyclobenzaprine (*Flexeril*) and carisoprodol (*Soma*).

Cyclobenzaprine is structurally related to the tricyclic antidepressants. Pharmacological studies in animals showed a similarity between the effects of cyclobenzaprine and the tricyclic antidepressants, including initial norepinephrine potentiation, potent peripheral and central anticholinergic effects, and inhibition of CNS neurotransmission. In addition, cyclobenzaprine may rarely potentiate serotonin syndrome in patients on an SSRI. Significant cyclobenzaprine ingestions may result in cardiovascular effects reminiscent of TCA overdoses. Treatment is usually supportive, but more aggressive measures as required in TCA overdoses are merited in patients with conduction abnormalities.

Carisoprodol is a centrally acting muscle relaxant that undergoes hepatic metabolism to its active metabolite, meprobamate. The parent compound and meprobamate are indirect GABAA receptor agonists which induce benzodiazepine-like effects. Recently, there has been an increase in carisoprodol being abused for its sedative effects and to augment the effects of other illicit drugs.

In addition to skeletal muscle-relaxing effects, carisoprodol also produces weak anticholinergic, antipyretic, and analgesic effects. Toxicity usually manifests as CNS depression which may progress to stupor, coma, shock, and respiratory depression. Alternatively, agitation and/or delirium may be the primary neurological manifestation of an overdose.

Carisoprodol intoxication may have manifestations like serotonin syndrome. Physical dependence has been described, and rapid withdrawal may result in anxiety, insomnia, irritability, headache, and muscle pain. Preparations of carisoprodol may include aspirin and codeine; therefore, it is important to ascertain the exact formulation ingested so treatment can be adjusted accordingly.

46.7.7 Organophosphates and Carbamates

Organophosphates and carbamates are found in many insecticides, pesticides, and some warfare nerve agents. Most exposures are accidental and often occur via the transdermal route; however, ingestion and inhalation can also occur.

Normally, acetylcholine is degraded by the enzyme acetylcholinesterase (AChE) found within plasma, red blood cells, and the neuromuscular junction. Organophosphates have a very high affinity to AChE and irreversibly phosphorylate acetylcholinesterase rendering it unable to further degrade acetylcholine. In the autonomic nervous system, acetylcholine accumulation leads to ganglionic nicotinic stimulation and postganglionic muscarinic stimulation. This stimulation leads to a myriad of autonomic findings with parasympa-

thetic effects predominating. In the somatic motor system, accumulation of acetylcholine in the neuromuscular junction leads to excessive nicotinic stimulation and ultimately to weakness, fasciculations, and paralysis.

Organophosphates phosphorylate acetylcholinesterase and render it unable to degrade acetylcholine. The relative excess of acetylcholine leads to nicotinic and muscarinic stimulation.

Carbamates are insecticides that produce similar toxicity but are distinguished from organophosphates by *reversibly* phosphorylating acetylcholinesterase. Unlike the organophosphate-AChE bond, this bond spontaneously hydrolyzes within 24 h. Carbamates also do not cross the blood-brain barrier as well as organophosphates and therefore produce less CNS effects.

Patients often present with a constellation of signs that create a toxidrome of cholinergic findings (Table 46.2). The mnemonic "DUMBBELLS" refers to diarrhea, urination, miosis, bronchorrhea and bronchospasm, emesis, lacrimation, lethargy, and salivation. The nicotinic signs include alteration in mental status, seizures, sweating, muscle fasciculations, weakness, and paralysis. Other symptoms include bradycardia, hypotension, and hypothermia. Plasma cholinesterase and red blood cell cholinesterase measurements are only useful in proving an exposure has occurred but do not correlate well with clinical severity.

Therapy in organophosphate poisoning begins with supportive care and maintaining the "ABCDs." Decontamination of the patient and protection of healthcare workers should take place concurrently. Adequacy of the airway, breathing, and circulation must be ensured. Charcoal can be used and gastric lavage considered if the mode of exposure was enteral.

High doses and a continuous infusion of atropine may be required for organophosphate poisoning. Tachycardia is not a contraindication for continued atropine therapy.

Antidote therapy consists of atropine and pralidoxime. Atropine is a selective muscarinic receptor blocker and therefore will reverse only muscarinic effects. Atropine does not bind to nicotinic receptors and will not be effective to reverse neuromuscular dysfunction such as weakness or overt paralysis. Very large doses of atropine may be required as it is a competitive antagonist. Doses of 0.05 mg/kg every 5 min may be required to achieve "atropinization," best defined as clearing of secretions. Mydriasis is an early indication of atropinization but is not an endpoint. Tachycardia is not a contraindication for continued atropine therapy. Continuous infusions of atropine may be required (0.02–0.08 mg/kg/h).

Pralidoxime helps restore acetylcholinesterase activity by competing for the phosphate moiety of the organophosphate-acetylcholinesterase complex, thereby causing release of acetylcholinesterase. Unlike atropine, it can treat neuromuscular dysfunction caused by organophosphate poisoning. It is important to begin pralidoxime early in the course of organophosphate poisoning as its use may reverse both hypermuscarinic and hypernicotinic effects. Untreated, the bond between the organophosphate and acetylcholinesterase "ages" and becomes refractory to pralidoxime therapy. There is evidence that pralidoxime may also aid in reversing the central nervous system effects. An initial dose of 25–50 mg/kg is given followed by a continuous infusion of 5–10 mg/kg/h in severe ingestions.

46.7.8 Alcohols

Ethanol is primarily eliminated through metabolism in the liver by alcohol dehydrogenase and is cleared from the blood for the most part by zero-order kinetics at rate of 10–25 mg/dL/h. This may be increased to above 30 mg/dL/h in chronic users. Blood levels above 100 mg/dL are consistent with intoxication, and levels above 500 mg/dL can be fatal. Most ethanol intoxications

occur among adolescents. Due to immature hepatic metabolism, small children are at increased risk for severe toxicity. Ethanol ingestions can lead to profound coma with respiratory depression, hypoglycemia (especially in small children), and an anion gap acidosis.

Ethanol ingestion in a small child = hypoglycemia until proven otherwise

Treatment is largely supportive with careful attention to identifying and treating hypoglycemia and co-ingestions. Hemodialysis clears ethanol at a rate 4–5 times greater than hepatic metabolism and should be considered in life-threatening overdoses.

Isopropyl alcohol creates an osmolar gap without an anion gap acidosis.

Isopropanol (isopropyl alcohol) is metabolized via alcohol dehydrogenase to acetone. Acetone is a nonacidic CNS depressant that is excreted by the kidneys and the lungs. Respiratory elimination accounts for the fruity smell of the breath in an intoxicated individual. Isopropanol is twice as potent an inebriant as ethanol; hence levels of 50 mg/dL produce intoxication. It is rapidly absorbed, and as little as 20 mL can induce symptoms. Large ingestions (plasma concentration >350 mg/dL) can lead to life-threatening central nervous system and myocardial depression. Unique to the ingestion of isopropyl alcohol is presence of an osmolar gap without anion gap acidosis. Treatment is supportive with attention to maintenance of the airway and hemodynamic integrity. Hemodialysis is reserved for patients with refractory hemodynamic instability that is generally seen with levels higher than 400 mg/dL.

Methanol and ethylene glycol can produce severe multisystem organ dysfunction. Methanol is found in fuels, solvents, windshield washing fluid, and paint products, while ethylene glycol is most commonly found in antifreeze and cleaners. The most common initial symptom for both ingestions is vomiting. Inebriation can occur with both but is more severe in ethylene glycol ingestions. With severe ingestions of either of these alcohols, an osmolar and anion gap acidosis ensues with resultant tachypnea, poor perfusion, and further depression in level of consciousness.

Ethylene glycol and methanol are metabolized in the liver by alcohol dehydrogenase to toxic metabolites.

Methanol and ethylene glycol are also metabolized by alcohol dehydrogenase. The metabolites of methanol and ethylene glycol have distinct toxicities. Ethylene glycol is metabolized by alcohol dehydrogenase to glycolic and oxalic acids. Oxalic acid combines with calcium and causes systemic hypocalcemia and the deposition of calcium oxalate crystals in tissues. Tetany and cardiac dysrhythmias may occur due to profound hypocalcemia. Late in the course, renal failure, cerebral edema, and seizures may occur due to calcium oxalate crystal deposition and the formation of toxic metabolites.

Ethylene glycol ingestion causes calcium oxalate crystal deposition in tissues and ultimately may lead to renal failure, dysrhythmias, and cerebral herniation.

Formic acid is produced by the metabolism of methanol. Formic acid directly inhibits mitochondrial respiration and is a potent ocular toxin. Visual disturbances that include blurry vision, decreased visual fields, and decreased acuity may occur. Examination may demonstrate dilated pupils unreactive to light and retinal edema with disc hyperemia. Visual changes are usually reversible, but blindness has been reported. Laboratory evaluation consists of alcohol level, serum electrolytes, creatinine, osmolality, blood urea nitrogen, and arterial blood gas analysis. As noted, both methanol and ethylene glycol will create an anion gap acidosis and osmolar gap.

Methanol toxicity leads to formation of formic acid and can lead to decreased visual fields and acuity.

Therapy for methanol and ethylene glycol toxicity includes supportive measures and correction of electrolyte and acid-base abnormalities.

There is little, if any, role for any gastrointestinal (GI) decontamination in alcohol ingestions due to:

- Rapid absorption of alcohol
- Risk for aspiration due to progressive obtundation
- Lack of absorption by activated charcoal

A rare exception would be in a patient with a massive methanol or ethylene glycol ingestion (e.g., suicide attempt) that occurred within 60 min of presentation. In these patients, gastric aspiration via flexible nasogastric tubing can be considered if the airway is protected.

Ethanol can be used as an antidote for methanol and ethylene glycol. Alcohol dehydrogenase has a higher affinity for ethanol than methanol or ethylene glycol. The administration of ethanol prevents the formation of the toxic metabolites of methanol and ethylene glycol.

Fomepizole is a competitive inhibitor of alcohol dehydrogenase.

Fomepizole is a competitive inhibitor of alcohol dehydrogenase and also prevents the metabolism of methanol and ethylene glycol to toxic end products. Advantages of fomepizole include the lack of ethanol-related side effects (inebriation, hypoglycemia) and its long half-life precluding the need for continuous infusion. Therapy with ethanol or fomepizole should be initiated for the symptomatic child with a methanol level over 20 mg/dL or an ethylene glycol level greater than 25 mg/dL. Fomepizole dosing is typically 15 mg/kg intravenously, followed by 10 mg/kg every 12 h.

Dialysis is indicated in methanol and ethylene glycol ingestions for renal failure, severe and refractory acidosis, visual impairment, and levels of methanol or ethylene glycol greater than 50 mg/dL.

Hemodialysis is highly effective for removal of alcohols and their metabolites. Indications for dialysis include refractory acidosis or end-organ damage (visual impairment, renal failure) regardless of level or a methanol or ethylene glycol level greater than 50 mg/dL. Therapeutic dosing of ethanol and fomepizole should be increased during dialysis as both antidotes are removed with hemodialysis. Lastly, there may be some benefit in administering thiamine and pyridoxine in ethylene glycol poisoning and folate in methanol poisoning to aid in shunting alcohol metabolism to less toxic pathways.

46.7.9 β-Blockers and Calcium Channel Blockers

β-Blockers and calcium channel blockers are two classes of cardioactive medications that have similar toxicity from overdose. Treatment of overdoses with either class of drug may be difficult due to refractory hemodynamic instability and can lead to significant morbidity and mortality.

β-Blockers inhibit the binding of epinephrine and norepinephrine to adrenergic receptors and therefore inhibit the many cellular responses of sympathetic stimulation. They possess potent negative chronotropic and inotropic properties. Calcium channel blockers also possess potent negative inotropic and chronotropic properties but do so by inhibiting calcium and sodium entry into cells. Both drug classes also produce smooth muscle relaxation further contributing to hemodynamic instability. Overdoses can present with hypotension, bradycardia, and signs of decreased cardiac output.

Patients with β-blocker overdoses may also present with mental status changes, coma, and seizures due to hypoglycemia. The ECG can demonstrate bradycardia, atrioventricular block, or ventricular arrhythmias. Management of β-blocker or calcium channel blocker overdose consists of supportive care with attention to the maintenance of organ perfusion. The determination of the serum glucose is especially important in β-blocker overdoses as hypoglycemia may occur early in the course. Activated charcoal should be given if presentation is less than 2 h, and whole bowel irrigation has been used in cases of sustained-release medications. Volume expansion, atropine, β-adrenergic agonists such as epinephrine, and calcium have been used with varied success.

Glucagon is a polypeptide hormone that is secreted by pancreatic alpha cells and acts to counter the effects of insulin. Glucagon has both positive inotropic and chronotropic activity due to its ability to increase intracellular cyclic

adenosine monophosphate (cAMP) synthesis. An initial dose of 0.05–0.15 mg/kg should be followed by an infusion of 0.05–0.1 mg/kg/h due to its short duration of action.

Hyperinsulinemic euglycemia therapy consists of a continuous insulin infusion while maintaining acceptable serum glucose levels by exogenous glucose administration. Limited studies have demonstrated improvement in blood pressure and metabolic acidosis utilizing this approach. Insulin therapy may improve hemodynamics due to increasing cardiac carbohydrate metabolism efficiency and its direct inotropic effects. Insulin infusion rates of 0.5–1 U/kg/h have been used, but close monitoring for prevention of hypoglycemia and hypokalemia is imperative. Intralipid emulsion therapy can be considered for refractory hemodynamic instability in lipophilic calcium channel or β-blocker intoxication.

Cardiac pacing, intra-aortic balloon pump, and extracorporeal myocardial support have also been used in severe poisonings refractory to the aforementioned therapies.

46.7.10 Clonidine

Clonidine is usually used as an antihypertensive medication but also is currently used in treatment of attention deficit hyperactivity disorder. It acts as a central α_2-adrenergic receptor agonist in the medulla oblongata. Central stimulation leads to decreased sympathetic output. Peripheral α-adrenergic stimulation can cause hypertension; however, this is short-lived and overshadowed by clonidine's sympathetic output inhibition. Clonidine has notable CNS depressant effects.

A single 0.1 mg tablet in toddlers or licking a clonidine patch can result in significant toxicity. Children often present with a depressed level of consciousness, miosis, and bradycardia with hypotension that can mimic narcotic overdose.

Children with a clonidine ingestion may present similarly to those with narcotic overdose.

The mainstay of therapy is supportive care. Respiratory support with mechanical ventilation may be required if profound CNS depression has occurred. Gastric decontamination is usually of little benefit as absorption has already occurred.

Naloxone has been used to reverse the respiratory and central nervous system depression with inconsistent results. Naloxone administered at a dose of 0.05 to 0.1 mg/kg (maximum single dose, 10 mg) has reversed the CNS and, to a lesser degree hemodynamic effects, of clonidine poisoning. If the child is responsive to naloxone therapy, repeated dosing or continuous infusions may be required due to its relatively short half-life. A recent case series suggested higher initial doses (6–10 mg) may be required to produce clinical improvement.

46.7.11 Digoxin

Digoxin toxicity can occur due to acute or chronic medication overdosage or after the ingestion of the oleander and foxglove plants. Digoxin acts to inhibit the sodium-potassium adenosine triphosphatase pump (Na^+-K^+ ATPase pump) leading to increased sodium and calcium influx into cells and potassium efflux from cells. This leads to increased inotropy in cardiac cells as well as decreased conduction velocity and increased vagal stimulation leading to slower heart rates.

Rhythm disturbances occur in digoxin poisoning and consist of atrioventricular block, ventricular ectopy, junctional ectopy, and ventricular tachycardia.

Hypokalemia, hypomagnesemia, and hypercalcemia may potentiate digoxin toxicity.

Many nonspecific symptoms may occur with acute digoxin ingestion. These include nausea, vomiting, drowsiness, weight loss, and visual changes including visual hues (usually yellow) and photophobia. Rhythm disturbances usually begin with sinus bradycardia which progresses to second- and third-degree heart block with ventricular ectopy, junctional ectopy, and ventricular tachycardia.

Following digoxin absorption, the distribution phase is very long. During the distribution phase, there is no strong correlation between tissue and serum levels. Therefore, serum digoxin levels may not correlate well with toxicity. Laboratory evaluation in acute digoxin overdoses may reveal hyperkalemia, whereas chronic overdoses can present with hypokalemia, particularly if there is concomitant diuretic use. Hypokalemia, hypomagnesemia, and hypercalcemia may all potentiate digoxin toxicity.

Management includes treatment of arrhythmias and electrolyte abnormalities and avoidance of vagal stimulation. Activated charcoal is recommended for ingestion of greater than 2 mg of digoxin in a child or 5 mg in an adolescent. Gastric lavage is contraindicated as vagal stimulation may precipitate arrhythmias. The preferred treatment for clinically significant arrhythmia or refractory hypotension is digoxin-specific antibody (Fab) fragments. Each vial of DigiFab contains 40 mg of Fab fragments and binds approximately 0.5 mg of digoxin. Dosing regiments are best made in conjunction with a medical toxicologist or a poison control center. Typically, children are empirically given five to ten vials. Atropine or cardiac pacing may improve sinus bradycardia and atrioventricular block.

46.7.12 Sympathomimetics

Cocaine, methylxanthines (including caffeine, theophylline, and aminophylline), and phenylalkylamine compounds represent the most common sympathomimetics encountered in clinical practice. The phenylalkylamines are a heterogeneous group of psychostimulant compounds which include methylenedioxymethamphetamine (also known as "MDMA," "ecstasy," or "Molly"), methylphenidate, ephedrine, amphetamines, phenylpropanolamine and cathinone, and a variety of synthetic cathinone-like designer drugs (also known as "bath salts"). Overdose with a synthetic cathinones differs from typical sympathomimetic toxicity mainly due to the prolonged duration of symptoms such as agitation, delirium, and psychosis.

These substances can be used illicitly or prescribed for such disorders as attention deficit hyperactivity disorder and narcolepsy. Sympathomimetic drugs are ingested, smoked, insufflated, or injected depending on the specific agent. These drugs generally increase the availability and activity of catecholamines and other monoamines by inhibiting the reuptake of synaptic adrenergic neurotransmitters, directly stimulating catecholamine release, or augmenting the postsynaptic functions of monoamine neurotransmitters.

Clinical presentation varies but typically includes cardiovascular and central nervous system disturbances. Patients often develop tachycardia, hypertension, and occasionally arrhythmias. Severe hypertension may be present and can lead to hemorrhagic strokes and myocardial ischemia. Central nervous system disturbances include fever, excitation, impaired sleep, changes in mood, agitation, anxiety, psychosis, and seizures.

β-Blockade may worsen hypertension in sympathomimetic ingestion due to unopposed α-adrenergic stimulation.

Therapy consists of supportive care. Severe hyperthermia should be treated with cooling measures, while seizures and agitation are best treated with benzodiazepines. Rhabdomyolysis may occur depending on the level of psychomotor agitation and is best treated by early and aggressive intravenous fluids. Hypertension typically improves with benzodiazepine administration but may

require the continuous infusion of nitroprusside or nitroglycerin. β-Blockade is contraindicated as it may leave unopposed α-adrenergic stimulation and worsen hypertension. Mechanical ventilation with sedation and neuromuscular blockade may be required in cases of life-threatening agitation and hyperthermia. Cases involving the ingestion of cocaine packets or balloons present the potential for the enteral release of lethal amounts of cocaine. These patients should undergo whole bowel irrigation in an ICU setting to ensure the rapid and complete passage of all packets.

46.7.13 Opioids and Synthetic Opioids

There has been a substantial increase in the availability of both prescribed and illicit opioids. Medications used to manage dependency such as buprenorphine/naloxone (Suboxone) and methadone have also become widely available. Illicit opioids of abuse such as fentanyl and heroin have become cheaper and endemic throughout the United States. Synthetic opioids such as α-fentanyl ("China White") and desomorphine ("krokodil") are particularly potent, and overdose is common. The explosive increase in the availability of opioids has led to a dramatic rise in pediatric intoxications. Opioid-related hospitalizations requiring PICU admission have more than doubled from 2004 to 2018.

Opioids are a heterogeneous group of compounds that exert their agonistic effects at mu, kappa, and delta opioid receptors. Mu receptor agonism is associated with the stereotypical effects of opioids: analgesia, miosis, CNS depression, and respiratory depression. Respiratory depression is the most dangerous feature of opioid overdose. Other signs and symptoms of opioid intoxication can include mydriasis, QT prolongation (associated with methadone), decreased gastrointestinal motility, and pulmonary edema. Ingestion of opioids with other CNS depressants, like ethanol and benzodiazepines, amplifies the CNS and respiratory depression effects of opioids.

Initial management of opioid intoxication involves rapidly addressing the airway, breathing, and circulatory needs of the patient while promptly administering the antidote naloxone. Naloxone is a competitive mu receptor antagonist that blocks and reverses the effects of opioids. Naloxone is very effective at reversing opioid-induced respiratory depression. While the intravenous route of administration is preferred, naloxone can be administered via the intraosseous, intramuscular, subcutaneous, endotracheal, inhalation, buccal, and sublingual routes. It has very low bioavailability via the oral route. In opioid-naïve patients, naloxone is dosed at 0.1 mg/kg IV for children <20 kg and at 2 mg IV for children ≥20 kg. This may be re-dosed every 3–5 min as needed. An infusion of naloxone may be necessary due to naloxone's short duration of action (30–60 min). Hourly infusion dose can be estimated by using two-thirds the bolus naloxone dose required to reverse respiratory depression.

In adolescents with suspected opioid addiction, smaller incremental naloxone doses should be used (0.04–0.4 mg per dose) to avoid precipitating withdrawal symptoms.

46.7.14 Cannabinoids and Synthetic Cannabinoids

The effects of marijuana are mediated largely by the effects of Δ-9 THC on cannabinoid receptors. The physical effects of marijuana include conjunctival hyperemia, tremor, emesis, mild hypertension, and tachycardia. Neurological effects include ataxia, lethargy, mydriasis, slowly reactive pupils, sedation,

coma, euphoria or dysphoria, hallucinations, psychosis, and stroke. Synthetic cannabinoids are also becoming increasingly popular drugs of abuse in adolescents. The more common product names include "K2" and "Spice." They are cannabinoid receptor agonists (structurally unrelated to THC) that bind to cannabinoid receptors with very high affinity. These drugs produce euphoria with mood and sensorium alterations. Adverse effects may be severe and include tachycardia, anxiety, paranoia, sedation, hallucinations, psychosis, and seizures. Long-term users are at risk for psychosis and neurocognitive problems.

Care of patients intoxicated with cannabinoids or synthetic cannabinoids is largely supportive with benzodiazepines being the preferred agent for treating agitation and seizures.

46.7.15 GHB (γ-Hydroxybutyrate)

Gamma-Hydroxybutyrate (GHB) has been used as therapy for narcolepsy and treatment for opioid and ethanol withdrawal. Recently, its illicit use has increased due to its mood-altering effects. GHB has been termed the "date rape drug" as it can cause rapid-onset central nervous system depression. GHB has a structure like γ-aminobutyric acid (GABA). It crosses the blood-brain barrier and indirectly interacts with opioid and GABA receptors promoting rapid eye movement (REM) and slow-wave sleep. At higher doses, greater anesthesia and myoclonic muscle activity occurs. In overdoses, patients typically present with severe central nervous system and respiratory depression. Many patients exhibit extreme agitation and combativeness between episodes of somnolence or obtundation. Self-injurious behavior has also been reported.

Supportive care is the mainstay of therapy. Occasionally endotracheal intubation and mechanical ventilation are required to support the respiratory and central nervous system depression. Reversal agents such as flumazenil and naloxone are rarely effective. Most patients recover with supportive care within 6–24 h.

46.7.16 Dextromethorphan

Dextromethorphan is present in common cough and cold preparations such as Robitussin DM and Coricidin. It is abused among adolescents due to over-the-counter availability and belief that it is safe. Common names used are "Triple C's," "roboshots," or "DXM."

Dextromethorphan is the D-isomer of the codeine synthetic analog, levorphanol, and binds sigma opioid receptors producing sedation. In higher doses, it inhibits the N-methyl-D-aspartate (NMDA) receptor and can precipitate central nervous system dysfunction including coma, agitation, euphoria, and hallucinations.

Dextromethorphan binds to opioid and NMDA receptors and can cause coma, euphoria, hallucinations, and agitation.

Common presenting signs and symptoms include tachycardia, hypertension, mydriasis, ataxia, and alterations in sensorium. The presentation may mimic anticholinergic poisoning and may precipitate serotonin syndrome. Pseudohyperchloremia may offer a clue to the diagnosis since dextromethorphan is prepared as a hydrobromide salt and standard laboratory tests cannot distinguish chloride ions from bromide ions. Bromide toxicity is possible with chronic abuse.

The management of dextromethorphan toxicity is largely supportive. Reversal of CNS symptoms with naloxone has been reported. The use of physostigmine to reverse concomitant anticholinergic toxicity is not recommended.

46.7.17 Caustics

Alkali caustics cause liquefaction necrosis, while acids coagulate proteins and cause tissue necrosis.

Caustics consist of acidic and alkali compounds often used as cleaning materials. Acids produce damage by coagulating proteins and causing tissue necrosis. Alkalis dissolve proteins and cause liquefaction necrosis.

Clinical manifestations consist of burns to the eyes, skin, mouth, oropharynx, esophagus, and stomach. Symptoms include pain, vomiting, drooling, or difficulty swallowing. Injuries to the esophagus may result in perforation and later strictures, while damage to the stomach may lead to ulceration and gastric outlet obstruction secondary to scarring of the pylorus. Respiratory symptoms may predominate if pulmonary aspiration has occurred. The extent of the injury is worse with prolonged contact, low pH (<2), and high pH (>12), or when highly concentrated agents are ingested.

Forced emesis, gastric lavage, and activated charcoal are contraindicated in caustic ingestions.

Surface decontamination is vital to decrease ongoing exposure to the toxin. Removal of clothing and copious flushing of eyes and skin should be done immediately. Forced emesis, gastric lavage, and activated charcoal are contraindicated. If any signs of upper airway obstruction are present, the airway should be secured using a critical airway protocol due to the likelihood of worsening edema. The gastrointestinal tract often is most severely injured and therefore requires careful assessment. The presence of oropharyngeal burns requires endoscopy to evaluate the possibility of distal injury. Children with even minor gastrointestinal burns upon presentation require very close follow-up as complications can occur weeks after the initial injury. Some children require repeated endoscopy with dilation to treat esophageal strictures. The use of corticosteroids remains controversial as consistent data demonstrating improved outcomes is lacking.

46.7.18 Hydrocarbons

Hydrocarbons are found throughout homes and account for 5% of all pediatric poisonings under 5 years of age.

Viscosity and volatility are important properties of hydrocarbons. Low-viscosity hydrocarbons have the greatest risk of aspiration, while highly volatile agents are likely to cause systemic toxicities.

Hydrocarbons are organic compounds that consist of solely carbon and hydrogen molecules. They have a variety of uses including industrial solvents, fuels, and household cleaners. Due to their ubiquitous nature, they are a significant cause of pediatric poisoning. Hydrocarbons account for approximately 5% of all poisonings in children less than 5 years of age.

Knowledge of the fundamental properties of hydrocarbons is essential to understanding their broad range of toxicities. Hydrocarbons have been classified based on two basic physiochemical properties: viscosity and volatility. Viscosity of a given substance is a measure of its ability to flow against friction. Low viscosity substances offer less resistance to flow and therefore spread easily. Saybolt seconds universal (SSU) is the time in seconds required for a substance to flow through a calibrated orifice. Substances with low viscosity (SSU < 60) spread rapidly along mucosa and represent the greatest risk of aspiration and lung injury, whereas high-viscosity substances (SSU > 200) do not spread quickly and therefore have minimal aspiration risk. Volatility is the ability of a substance to vaporize. Highly volatile substances quickly enter the systemic circulation and central nervous system and cause significant systemic toxicity.

Classification of hydrocarbons using viscosity and volatility can aid in determining expected clinical effects:

Low Viscosity – Low Volatility Produce mainly pulmonary complications if aspirated with little or no systemic effects (e.g., mineral seal oil, furniture oils, and polishes). Pulmonary aspiration of low-viscosity substances causes chemical

pneumonitis and denaturation of surfactant. An acute respiratory distress cascade ensues with the development of poorly compliant lungs and compromised gas exchange.

Intermediate Viscosity – Intermediate Volatility Can produce both pulmonary and systemic/CNS toxicity. The dominant toxicity may depend on the amount and route of exposure (ingestion, aspiration, inhalation). Most hydrocarbons fall into this category (e.g., gasoline, kerosene, lighter fluid).

High Volatility Produce multisystem dysfunction such as hepatotoxicity, nephrotoxicity, cardiotoxicity, and CNS complications. Aromatic hydrocarbons and chlorinated hydrocarbons comprise most of this group (e.g., toluene, xylene, benzene, methylene chloride, carbon tetrachloride, trichloroethylene). These compounds are used as solvents and spot removers. Naphthas are mixtures of aromatic and aliphatic hydrocarbons that also can be highly volatile.

High Viscosity and Low Volatility Produce little to no risk for either pulmonary or systemic toxicity unless large quantities ingested or aspirated. (i.e., baby oil, petroleum jelly, mineral oil, motor oil, transmission fluid).

Serial examinations are essential in the supportive care of children with hydrocarbon exposures. Children should be carefully monitored and remain NPO. Forced emesis, activated charcoal, and gastric lavage are strongly contraindicated due to the increased risk of aspiration.

Treatment may include stabilization of the airway and mechanical ventilation to provide appropriate gas exchange. Nebulized bronchodilators should be initiated if bronchospasm is observed. Intravenous beta-agonists should be avoided as the myocardium may be prone to arrhythmia following hydrocarbon ingestion. If intubation and ventilation are necessary, PEEP should be titrated to maintain oxygenation. High-frequency oscillatory ventilation and artificial surfactant preparations have theoretical benefit and should be considered in refractory cases. Respiratory extracorporeal membrane oxygenation is a therapeutic option for severe hypoxemia unresponsive to conventional mechanical ventilation. There is no role for steroids or routine prophylactic antimicrobials.

46.7.19 Carbon Monoxide

Carbon monoxide prevents oxygen binding to and release from hemoglobin and other heme-containing molecules which results in tissue hypoxia.

Carbon monoxide (CO) is an odorless, tasteless, and colorless gas that is caused by the incomplete combustion of carbon-containing substances. Common sources of CO poisoning include fire, engine exhaust, and faulty household furnaces. Most household exposures occur in the wintertime due to faulty exhaust from combustion heating systems. CO binds to hemoglobin with a 250-fold higher affinity than oxygen. When bound to hemoglobin, CO occupies an oxygen binding site and stabilizes the hemoglobin tetramer which shifts the oxygen-hemoglobin dissociation curve to the left restricting the release of transported oxygen to bodily tissues. The result is reduced oxygen delivery to body tissues, tissue hypoxia, and associated anaerobic metabolism. These effects on hemoglobin are greater in infants because CO binds more tightly to fetal than adult hemoglobin. CO also binds to and impairs the functions of other endogenous heme-containing molecules, including myoglobin and the mitochondrial enzymes of oxidative phosphorylation within the electron transport chain. This amplifies the effects of poor oxygen delivery at the cellular level by impairing cellular oxygen utilization and ATP synthesis. Free

radical-associated reperfusion injury is hypothesized to play a part in the delayed toxicity of CO poisoning in those that survive exposure. The brain and cardiac tissues are the body tissues that are most affected by carbon monoxide poisoning because of their higher metabolic rate and oxygen demand.

Symptoms of CO toxicity are markedly variable depending on the exposure and the presence of comorbidities. Early symptoms are nonspecific and include headache, dizziness, nausea/vomiting, light-headedness, and shortness of breath. Later symptoms include altered mental status, confusion, syncope, seizure, stroke-like symptoms, metabolic acidosis, and coma. In infants, CO poisoning may present as a brief, resolved, unexplained event.

Diagnosis begins with the clinical suspicion of toxicity given historical and physical examination findings and requires confirmation with spectrophotometric co-oximetry measured via a blood sample. While noninvasive pulse co-oximeters do exist and their use is convenient for field screening and rapid triage, their accuracy is insufficient to diagnose CO toxicity alone. Individual baseline CO levels can vary depending on environmental exposures with typical levels being less than 3%. Smokers can have baseline levels around 10%. Low carboxyhemoglobin levels (<15–20%) correlate well with mild symptoms such as nausea, vomiting, and headache. Levels greater than 60–70% are usually rapidly fatal. Between those carboxyhemoglobin ranges, the severity of symptoms does not necessarily correlate with CO levels and requires clinical correlation. Other testing that may be beneficial for patients presenting with CO toxicity include a 12-lead EKG, a complete blood count, chemistry, lactate, troponins, creatine phosphokinase, blood cyanide testing for patients with profound acidosis, and brain imaging for patients with altered mental status.

Management of CO toxicity primarily consists of removing the patient from the environment and administration of 100% oxygen. The half-life of carboxyhemoglobin in room air is approximately 5 h, whereas the half-life in 100% FiO_2 oxygen is approximately 1 h. Consequently, 4–6 h of normobaric oxygen at an FiO_2 of 1.0 will remove greater than 90% of the CO. Management of CO toxicity with hyperbaric oxygen (HBO) therapy is controversial. HBO is appealing because it can further reduce the half-life of carboxyhemoglobin to 20 min.

Accepted criteria for the use of HBO in CO poisoning include:

- CO level > 25 percent
- CO level > 20 percent in pregnant patient
- Coma
- Severe metabolic acidosis (pH < 7.1)
- Evidence of end-organ ischemia

Some evidence exists that HBO may improve long-term neurocognitive outcomes in CO poisoning. Benefits of HBO may be offset by the limited availability of appropriately sized and equipped hyperbaric chambers. Prolonged transport may preclude effective HBO treatment. Possible complications of HBO therapy include barotrauma, seizures, pulmonary edema, or claustrophobia.

46.7.20 Cyanide Toxicity

Cyanide (CN) poisoning is a rapidly lethal poisoning that is uncommon but must be rapidly recognized for treatment to be successful. In the United States, CN poisoning is most commonly associated with exposure to burning plastics and other synthetics encountered during domestic fires. It is common for CN toxicity to accompany CO toxicity in this setting. Industrial CN exposures are more common for adult patients than pediatric patients and often occur in the

context of manufacturing, metal work, and textile industries. Medical exposures can occur from CN liberation and accumulation with sodium nitroprusside infusion. Case reports exist of CN toxicity from exposures to cyanogenic compounds, including amygdalin that is found within the bitter almond, peach, and apricot kernels.

Normally, the small amounts of CN encountered in the environment are metabolized in muscle and liver by the enzyme rhodanese which uses thiosulfate to convert CN to nontoxic thiocyanate. Thiocyanate is then readily excreted in the urine. In a toxic exposure, CN accumulates and binds avidly to and inhibits cytochrome a_3 in the electron transport chain which uncouples mitochondrial oxidative phosphorylation. Consequently, oxygen delivered to tissue is unable to be utilized resulting in cellular anoxia and anaerobic metabolism. The brain and myocardium are particularly vulnerable to cellular anoxia because of their baseline high metabolic and oxygen demands.

Early symptoms include headache, diaphoresis, dizziness, nausea, vomiting, tachypnea, hyperpnea, and flushing. Flushing, or "cherry red" skin color, is secondary elevated venous oxygen tension caused by poor capillary oxygen extraction. The breath may have the odor of "bitter almonds" in patients with cyanide poisoning. Later symptoms include seizure, coma, respiratory failure, and cardiac arrest.

The diagnosis of CN toxicity requires a clinical suspicion, physical examination findings, and corroborating laboratory evidence. Blood CN concentrations are not readily available to be clinically useful but provide confirmation of the diagnosis. Serum cyanide levels of 0.5–1.0 mg/L correlate to milder symptoms, including tachypnea, hyperpnea, tachycardia, flushing, dizziness, nausea, and vomiting. Levels from 1.0 mg/L to 2.5 mg/L are associated with obtundation, and levels greater than 2.5 are associated with comatose state and cardiac arrest.

The diagnosis of cyanide toxicity requires clinical correlation but often occurs as a result of fire exposure in an enclosed area and often presents with a severely elevated serum lactate (>10 mmol/L).

Laboratory studies that may aid in the diagnosis of CN toxicity include carboxyhemoglobin and methemoglobin levels, serum lactate, and central venous blood gas analysis. A serum lactate >10 mmol/L in a victim of a house fire has high sensitivity and specificity for CN toxicity. CN toxicity causes a decrease in the SaO_2–SvO_2 difference owing to poor oxygen extraction at the tissue level. Diagnostic testing should also include a 12-lead EKG, a complete blood count, chemistry, troponins, creatine phosphokinase, and brain imaging for patients with altered mental status.

Therapy must be initiated promptly and often empirically. CN antidotal therapy attempts to detoxify CN using three possible mechanisms: inducing methemoglobinemia, binding cyanide, and providing thiol substrate to serve as sulfur donors.

The traditional cyanide antidote kit in the United States consisted of amyl nitrite (in 0.3 mL ampules) and sodium nitrite (in 300 mg/10 mL ampules). The amyl nitrite is intended for inhaled administration on scene until IV access is obtained. Administering nitrites converts hemoglobin into methemoglobin, which has a high affinity for CN and causes the CN to dissociate from cytochrome oxidase. However, nitrite administration is associated with hypotension and is contraindicated in patients with concomitant CO poisoning or a history of G6PD. Due to concerns of excessive methemoglobinemia and an unfavorable safety profile, hydroxocobalamin is preferable therapy in children.

Hydroxocobalamin, a vitamin B12 precursor, avidly binds to intracellular cyanide with a greater affinity than cyanide has for cytochrome oxidase. By competitively binding cyanide, it acts to restore oxidative phosphorylation. It detoxifies CN without the need to induce methemoglobinemia. Hydroxocobalamin acts rapidly, has few adverse effects, and can be used in patients with concomi-

tant CO poisoning making it an ideal agent for empiric use in children with smoke inhalation who are suspected to have cyanide toxicity.

The dose is typically 70 mg/kg with a maximum of 5 g IV. Side effects include reddening of the skin and bodily fluids which can last for 2–3 days and may also interfere with routine laboratory spectrophotometric analyses. Rash, headache, nausea, and transient hypertension are also possible side effects.

Sodium thiosulfate provides sulfur donors for rhodanese, a ubiquitous enzyme that detoxifies cyanide. Sulfonated rhodanese promotes the conversion of cyanide to the far less toxic and renally excreted thiocyanate. Side effects can occur at higher serum thiocyanate levels and include arthralgia, nausea, hypotension, and injection site discomfort.

46.7.21 Methemoglobinemia

Methemoglobin is hemoglobin with the iron oxidized to the Fe2+ state which impairs the oxygen-carrying capacity of hemoglobin.

Methemoglobin is a form of hemoglobin that is produced when the ferric (Fe^{3+}) iron of the heme moiety is oxidized to the ferrous (Fe^{2+}) state. This results in a conformational shift in the hemoglobin molecule which renders the hemoglobin unable to bind oxygen, causing a leftward shift in the oxygen-hemoglobin dissociation curve. Impaired hemoglobin oxygen-carrying capacity leads to decreased tissue oxygen delivery, tissue hypoxia, and tissue anaerobic metabolism. Children, particularly infants, are at greater risk for methemoglobinemia than adolescents and adults because of reduced erythrocyte cytochrome B5 methemoglobin oxidase activity and the greater susceptibility of fetal hemoglobin to oxidative changes of nitrites than adult hemoglobin. Infants and young children also have a greater abundance of GI flora due to a relatively higher gastric pH that allows greater intestinal conversion of dietary nitrates to oxidative nitrites.

Medications with oxidative effects are the most common cause of methemoglobinemia. The most common of these methemoglobin-inducing medications include the local anesthetics, particularly benzocaine and prilocaine. Antibiotics such as dapsone and pharmaceutical nitrites have been implicated in inducing methemoglobinemia. Non-pharmacological causes include dietary nitrates, particularly those arising from contaminated water supplies.

Signs and symptoms of methemoglobinemia vary with the degree of methemoglobinemia and the underlying comorbidities of the patient. Cyanosis is the most common and distinguishing feature of methemoglobinemia and becomes apparent clinically when methemoglobin levels approach 1.5 g/dL (10–20% of total hemoglobin). Infants and young children can exhibit cyanosis at methemoglobin concentrations of as low as 3%. Other symptoms reflect cardiopulmonary and central nervous system effects of hypoxia and include dyspnea, tachycardia, light-headedness, syncope, and altered mental status. The physical appearance of blood also assumes an increasing brownish/chocolate color as the methemoglobin levels increase.

As the percent of methemoglobin increases, the oxygen saturation measured by standard dual-wavelength pulse oximetry trends toward and remains around 85%. A significant difference between the oxygen saturation on standard pulse oximetry and the calculated oxygen saturation on a blood gas analysis is referred to as a "saturation gap" and supports the diagnosis of methemoglobinemia.

Since pulse oximetry does not distinguish among the different types of hemoglobin, co-oximetry is required to confirm methemoglobinemia. A co-oximeter measures concentration of oxygenated hemoglobin, deoxygenated hemoglobin, carboxyhemoglobin, and methemoglobin as a percentage of the

total hemoglobin concentration in the blood sample. Use of co-oximetry is indicated when hypoxia is possibly due to a toxin exposure or when hypoxia fails to improve with the administration of oxygen. Co-oximetry or direct measurement of serum methemoglobin confirms methemoglobinemia and provides the percentage of methemoglobin present prior to therapy.

The oxygen saturations in methemoglobinemia often register around 85% with dual-wavelength pulse oximetry because of the absorptive properties of methemoglobin.

Normal methemoglobin percentage is 1% (range 0–3%). Symptoms associated with higher percentage of methemoglobin are as follows:

- 3–10% – Slight discoloration (e.g., pale, gray, blue) of the skin
- 10–20% – Increasing asymptomatic cyanosis
- 20–30% – Anxiety, headache
- 30–50% – Dyspnea, light-headedness, weakness, confusion, palpitations, chest pain
- 50–70% – Arrhythmia, delirium, seizures, coma, profound acidosis
- >70% – Usually, death

An oxygen saturation gap (the difference between the oxygen saturation measured on a blood gas sample and that measured on standard pulse oximetry) suggests methemoglobinemia.

Treatment of methemoglobinemia begins with withdrawing the offending agent and providing routine supportive care. Definitive treatment involves reducing the ferrous iron of hemoglobin back to its native ferric state with methylene blue (MB) or ascorbic acid.

Symptomatic children (cyanosis, impaired CNS, and acidosis) or asymptomatic children with methemoglobin level >20 percent require treatment. A single dose of MB acts rapidly within 10–60 min, whereas treatment with ascorbic acid requires multiple doses and may take 24 or more hours to effectively reduce methemoglobin levels.

Typically, 1 mg/kg of 1% methylene blue is given orally or intravenously. It may be re-dosed if needed, but cumulative doses should not exceed 7 mL/kg. Side effects of methylene blue treatment include systemic and pulmonary hypertension, restlessness, dyspnea, nausea, vomiting, tremulousness, diaphoresis, thrombophlebitis, and anaphylaxis. Refractory methemoglobinemia may be treated with sodium ascorbate, blood transfusions, or exchange transfusion.

Methemoglobinemia is treated with methylene blue or ascorbic acid.

Ascorbic acid (vitamin C), an alternative reducing agent, can be used when methylene blue is unavailable or contraindicated (e.g., children suspected or proven G6PD).

Review Questions

1. A 14-year-old male is found unresponsive in his room by his mother. EMS is called and transports the teenager to the nearest emergency department. On examination, the patient responds to painful stimulation and moves all extremities symmetrically. He does not follow any commands. Laboratory evaluation shows a serum Na^+ of 140 mEq/L, K^+ 4.0 mEq/L, chloride 105 mEq/L, HCO_3^- 27 mEq/L, glucose 100 mg/dL, and BUN 15. The measured serum osmolality is 310 mOsm. Which of the following ingestions is most likely?
   A. Ethanol
   B. Ethylene glycol
   C. Methanol
   D. Isopropyl alcohol
   E. Salicylates

2. A 5-year-old girl has been outside playing in a barn. She is found an hour later by her father. She is somnolent, diaphoretic, and salivating and has some twitching of her muscles. On arrival at the hospital, she has emesis and requires endotracheal intubation for airway protection. What is the likely ingestion?
   A. Amphetamine
   B. Imipramine

C. Organophosphate
D. Salicylate
E. Thioridazine

3. A 15-year-old female who presents to the emergency department after ingesting an unknown quantity of unknown pills approximately 2 h ago. She has a pulse of 68 and blood pressure of 78/32. Her respiratory rate is 14 and unlabored and has a room air oxygen saturation of 97%. She is somnolent but easily arouses. On ECG she has a QRS interval of 160 ms and QT on of 0.55 s She is receiving a NS fluid bolus but is having persistent hypotension and occasional ventricular ectopy. The most important therapy that should be initiated promptly is:
   A. Atropine
   B. Endotracheal intubation
   C. Epinephrine
   D. Lidocaine
   E. Sodium bicarbonate

4. Exposure to which of the following hydrocarbons would likely produce little or no pulmonary or systemic toxicities unless large quantities were ingested?
   A. Benzene
   B. Furniture oils and polishes
   C. Gasoline
   D. Kerosene
   E. Motor oil

5. An 18-year-old male is brought to the emergency department by his friends after ingesting "a bottle" of Tylenol the previous evening. On exam the patient is uncooperative but has no abnormal findings on exam. Laboratory values reveal an anion gap of 15, ethanol level of 0.10%, normal coagulation profile, normal hepatic enzymes, and an acetaminophen level of 16 mcg/mL. Appropriate initial treatment is:
   A. Admit, begin N-acetylcysteine therapy immediately.
   B. Admit, repeat acetaminophen level in 4 h.
   C. Admit, repeat ethanol and acetaminophen level in 4 h.
   D. Admit, repeat ethanol, liver enzymes, and acetaminophen level in 4 h.
   E. Repeat acetaminophen level in 4 h, discharge if level < 10 mcg/mL.

6. A 16-year-old female is admitted to the PICU for ongoing N-acetylcysteine therapy due to a toxic acetaminophen level at 4 h. By report she has ingested 25,500-mg acetaminophen gel caps, 10,400-mg ibuprofen tablets, an unknown quantity of cyclobenzaprine, 5 10-mg prednisone tablets, and 24 oz of beer. She has been uncooperative throughout her treatment in the emergency department. Upon arrival to the PICU, she is mildly febrile, has no increased work of breathing, and has excellent perfusion in NSR. Other pertinent exam findings include facial flushing and mydriasis. Her neurological exam reveals no focal deficits, but she continues to be uncooperative and displays bizarre behavior claiming "ants are crawling all over me."
   The most likely cause of her current neurological symptoms is:
   A. Acute ethanol intoxication
   B. Acute steroid psychosis
   C. Anticholinergic effects of cyclobenzaprine
   D. Hepatic encephalopathy due to massive acetaminophen ingestion
   E. Unreported co-ingestion

7. Which overdose is matched most correctly with its mechanism of action and its clinical effects?
   A. Carisoprodol – indirect NMDA receptor agonist causing anticholinergic, antipyretic, and analgesic effects
   B. Clonidine – peripheral α_2-adrenergic receptor antagonist causing hypotension and bradycardia
   C. Cyclobenzaprine – norepinephrine inhibition and central cholinergic effects causing hypotension and neuroexcitability
   D. Dextromethorphan – binds to opioid and NMDA receptors causing coma, euphoria, hallucinations, and agitation
   E. Digoxin – inhibits Na^+-K^+ ATPase pump causing increased inotropy and increased chronotropy

Answers

1. D
2. C
3. E
4. E
5. A
6. C
7. D

Suggested Reading

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The Approach to the Critically Ill Infant

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Learning Objectives

- Appreciate the unique physiologic state of transition that occurs in the neonatal period.
- Describe key anatomic and physiologic differences between the small infant and older child and how they may affect critical care management.
- Describe the rapid cardiopulmonary assessment and stabilization of the infant presenting in extremis.
- Provide a brief description of intravenous access points for infants.
- Utilizing key physical examination findings, be able to quickly narrow diagnostic possibilities to allow the timely initiation of specific therapies.
- Provide an initial laboratory and imaging assessment in critically ill infants and subsequent testing based on specific diagnostic considerations.
- Provide brief clinical summaries of life-threatening diseases affecting neonates and infants.
  (i) Neonatal sepsis
  (ii) Congenital heart disease
  (iii) Abusive head trauma in infancy
  (iv) Inborn errors of metabolism
  (v) Infantile botulism
  (vi) Methemoglobinemia
  (vii) Hemorrhagic shock and encephalopathy syndrome

47.1 Introduction

This chapter will focus on infants less than 90 days of age who present with an acute decompensation. An overview of important physiologic and anatomic considerations in infancy will be reviewed. An expanded pediatric advanced life support (PALS) approach will be utilized for the initial stabilization and management of the critically ill infant. Lastly, synopses of selected disorders that can cause life-threatening illness in the small infant will be provided.

47.2 Infant Anatomic and Physiologic Considerations

47.2.1 Airway

There are important anatomic and functional differences between the airway of a small infant and older child. A clear understanding of these developmental differences enables the clinician to adeptly manage the infant airway during critical illness.

The infant airway is prone to dynamic obstruction and is poorly tolerant of mucosal edema.

Several characteristics of the infant airway increase the risk for upper airway obstruction. The prominent occiput of the infant causes flexion at the neck when lying supine (Fig. 47.1). The tongue is proportionally larger, and the epiglottis and soft tissues of the upper airway are more compliant. The more anterior and cephalad (C3–C4 vs. C4–C5 in an adult) infant larynx is cone shaped and does not assume its cylindrical shape until approximately 8 years of age. All these factors add to the infant's propensity for upper airway obstruction. In addition, mucosal edema of the airway is poorly tolerated. The narrowest part of the infant airway is at the cricoid ring in contrast to the vocal cord aperture in adults. Resistance to airflow is inversely proportional to the fourth power of the radius of the airway; consequently, 1 mm of concentric edema at the level of the cricoid ring increases resistance 16 times.

Due to the relatively large tongue and a large epiglottis that nearly touches the soft palate, infants are obligate nose breathers. Nasal passages may become

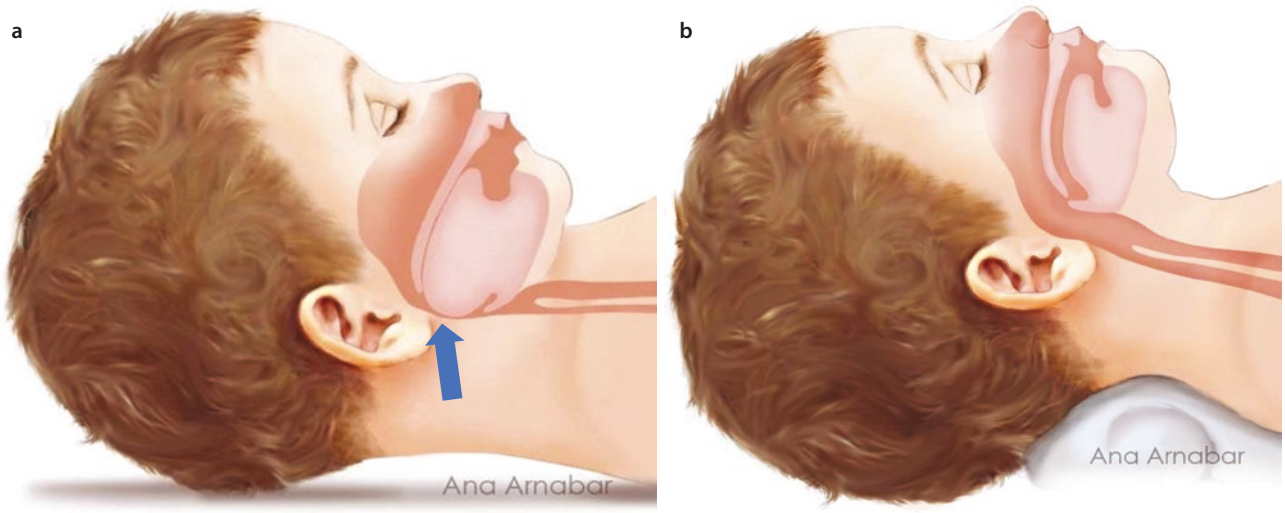

Fig. 47.1 **a** Occipital prominence causing flexion and upper airway obstruction (*arrow*). **b** Proper positioning offsets occipital prominence and opens airway

completely or partially obstructed with mucous, edema, or a large nasogastric tube. A significant portion of infants are unable to breathe orally when the nasal passages are occluded. Infants with thick rhinorrhea may display signs of upper airway obstruction despite a patent oropharyngeal airway.

47.2.2 Breathing

The diagnosis and management of respiratory insufficiency in the small infant require a clear understanding of the developmental anatomy and physiology of the thorax and lungs. The relationship between functional residual capacity and closing volume must be appreciated to understand the unique conditions found in the infant chest.

47.2.2.1 Lung Volumes

Functional residual capacity (FRC), the volume of gas in the lung at the end of tidal breathing, is reached when the inward forces of the lung balance the outward forces of the chest wall. Several features of the infant chest create a propensity toward a decreased FRC. Although the compliance of the infant lung is similar to that seen in the older child, the chest wall is far more compliant due to a cartilaginous rib cage and poor muscular development. The highly compliant chest wall has little outward elastic recoil. Therefore, the force to balance the inward recoil of the lung is insufficient, and hence there is a tendency toward alveolar collapse (atelectasis) and a reduction in FRC.

The interplay between the highly compliant chest wall and infant lung has important implications on lung volumes. *Closing volume* (CV) is the volume above residual volume at which the small airways begin to collapse. *Closing capacity* (CC) is the sum of residual volume and closing volume at which the small airways close during expiration.

The highly compliant chest wall and the natural inward recoil of the infant lung create a propensity toward atelectasis.

Due to the highly compliant chest wall with poor elastic properties, the infant's closing volume is greater than the predicted FRC. The *predicted* FRC of 25–30 mL/kg is lower than the closing capacity of 35 mL/kg. Without compensation, terminal airway closure would occur during normal tidal breathing (Fig. 47.2). Indeed, this occurs when an infant's muscle tone is reduced (e.g., general anesthesia). However, this does not occur during normal tidal breath-

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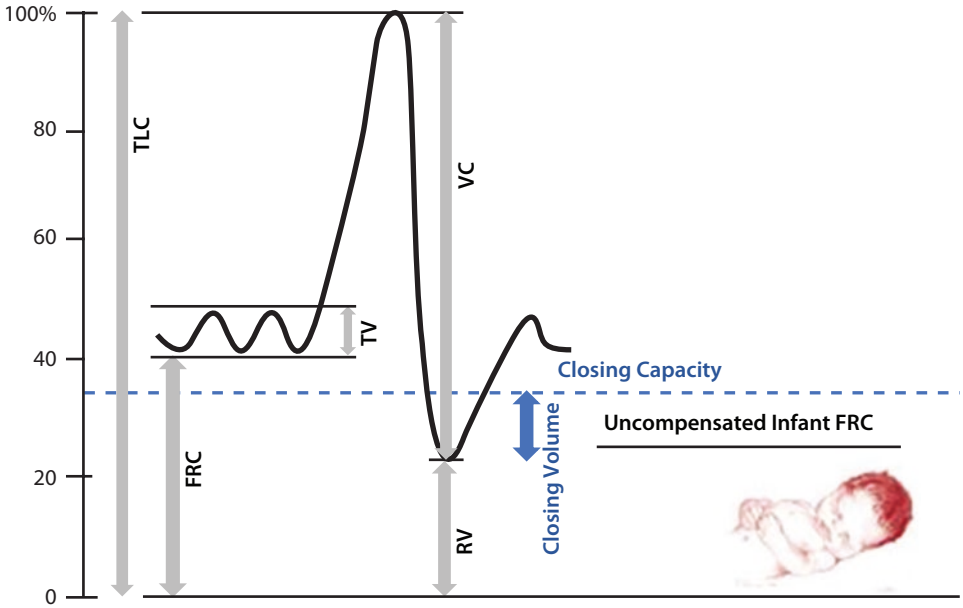


Fig. 47.2 Lung volumes demonstrating infant's uncompensated FRC less than closing capacity. TLC total lung capacity, FRC functional residual capacity, RV residual volume, VC vital capacity

Infants require developmental compensatory mechanisms to maintain FRC above closing capacity.

ing due to several inherent compensatory mechanisms. The baseline increased minute ventilation of the small infant allows for short expiratory times resulting in the maintenance of intrinsic positive end-expiratory pressure (PEEP). The phenomenon of laryngeal braking also prevents small airway collapse. Laryngeal braking refers to early glottic closure ceasing expiration prior to reaching closing volume and, thus, maintaining FRC greater than closing capacity. Lastly, respiratory muscle and diaphragmatic tonicity during exhalation also help to maintain FRC in a small infant. These mechanisms that create a "dynamic FRC" rather than a "relaxed FRC" remain in place until approximately 6–12 months of age.

47.2.2.2 Oxygen Metabolism

In addition to lung volumes, infants display considerable differences in oxygen metabolism compared with the older child. Oxygen consumption is approximately 7 mL/kg/min at birth compared to 4 mL/kg/min in older children and adults. The metabolic cost of respiration work is higher in infants and may account for 15% of total oxygen consumption. Although tidal volume is similar as adults (6–7 mL/kg), the respiratory rate of infants is higher to achieve an appropriate minute ventilation to meet the high metabolic demands of infants.

47.2.2.3 Airway Resistance

The major site of airway resistance in the adult is in the upper airway, accounting for 80% of total resistance. In contrast, due to the large cross-sectional surface area of peripheral airways, flow occurs with little resistance. Infants lack the large cross-sectional area of the distal airways, and thus, a much larger portion of total airway resistance occurs in the periphery (approximately 50%). This observation is consistent with clinical observations of lower airway edema and inflammation causing severe disease in infants versus older children (i.e., bronchiolitis). Some authors refute the large contribution of the peripheral airways on total resistance and claim, like the adult, the major site of resistance is the upper airway. Regardless, because the absolute diameter of the infant's peripheral airways is small, any decrease in the radii of the lower airway is poorly tolerated.

47.2.2.4 Respiratory Muscles

During periods of increased work of breathing, respiratory failure may ensue earlier in infants due to immaturity of the diaphragm and intercostal muscle. Type I muscle fibers have a high oxidative capacity and are important in sustained repeated muscle contraction. The small infant has approximately half the density of these fibers when compared to the older child and is, therefore, at greater risk for early respiratory fatigue. Infants may have a higher degree of respiratory muscle inefficiency leading to muscle ischemia at high respiratory rates.

The inherent differences in lung–chest wall dynamics, oxygen metabolism, and respiratory musculature place the small infant at greater risk for respiratory insufficiency than the older child and adult.

47.2.3 Cardiovascular

47.2.3.1 Intrauterine to Extrauterine Transition

Key events in the transition from the intrauterine to extrauterine cardiovascular function are a result of aeration and oxygenation of the newborn lung and the subsequent changes in vascular pressures. With the first breath, the pulmonary vasculature becomes suspended and dilated due to the sudden increase in lung volume and oxygen tension. The sudden fall in pulmonary vascular resistance causes an increase in pulmonary blood flow and, subsequently, a rise in pulmonary venous return to the left atrium. The increase in left atrial volume and pressure causes the flap of the foramen ovale to close against the secundum atrial septum. The rising oxygen tension also initiates closure of the ductus arteriosus. The closure of the ductus arteriosus occurs in 98% of infants by day 4 of life. With completion of these events, the newborn heart functions as two circulations (pulmonary and systemic) in series.

It is often during these transitional events that congenital heart disease may become apparent. Persistent patency of the ductus arteriosus, and to a lesser extent the foramen ovale, can lead to clinically significant shunting. The nature of the shunt can be predominantly left to right, right to left, or bi-directional depending upon underlying anatomy and hemodynamics. Failure of the pulmonary vasculature to relax can result in pulmonary hypertension.

Key events in the transition from fetal to neonatal circulation include a fall in pulmonary vascular resistance, closure of the foramen ovale, and constriction of the ductus arteriosus.

47.2.3.2 Developmental Considerations

The cellular composition of the newborn myocardium infers important cardiovascular consequences. The neonatal myocardium is composed of poorly organized myocytes that have approximately half the number of contractile elements (actin, myosin, troponin, tropomyosin) seen in a mature heart. These myocytes have a functionally immature sarcoplasmic reticulum that cannot provide sufficient cytosolic calcium; hence the immature myocardium has a greater reliance on extracellular calcium entering via ion channels. This explains the greater inotropic response to exogenous calcium and digitalis seen in newborns when compared to adults.

Autonomic innervation of the myocardium is also functionally immature. Although the density of β-adrenergic receptors is high, β-receptor–adenylate cyclase coupling mechanisms are inefficient. Vagal innervation of the myocardium is complete at birth leading to a state of parasympathetic dominance.

The ongoing development of the myocardium results in an infant with a poorly compliant ventricle that has limited responsiveness to increasing preload. The relative inability to increase stroke volume during states where increased cardiac output is required leads to a state of chronotropic dependence. Fortunately, infants are generally tolerant of tachycardia during periods of increased metabolic demand. This dependence on heart rate to maintain cardiac output is especially noteworthy when considering the infant's vulnerability to bradycardia during vagal stimuli.

The neonatal myocardium has less contractile potential, is more reliant on chronotropy and intracellular calcium, and has greater parasympathetic tone than the mature myocardium.

Despite the ongoing development of the cardiovascular system, the infant maintains an impressive baseline cardiac output to meet its high metabolic demand. Although the absolute cardiac output as measured in L/min is low as compared to an adult, the cardiac output in relation to body size is higher in the neonate, measuring up to 4 L/min/m^2 as compared to 2.5–3.5 L/min/m^2 in the adult.

47.2.4 Central Nervous System

The infant brain is in a phase of rapid cellular development. Although infants possess a similar number of neuronal cells as adults, neurotransmission remains functionally immature due to ongoing axonal and dendritic growth. Glial cells (astrocytes, oligodendrocytes) continue to multiply well into the second year of life. These cells serve as neuronal support and are important in myelination. Myelination of axons is an ongoing process that begins early in prenatal life and extends to 6 years of age. As myelination advances in a rostrocaudal fashion, axonal impulse transmission becomes more efficient.

Open fontanels do not impart full protection against the untoward effects of intracranial hypertension.

A major distinction from a gross anatomical basis is the presence of open fontanels in the small infant (Fig. 47.3). The anterior fontanel remains open until 12–24 months, whereas the posterior fontanel closes by 2–4 months. A misconception is that due to the presence of open fontanels, infants can tolerate increases in intracranial pressures without untoward consequences. This may in part be true in cases of slowly evolving intracranial hypertension as may occur in chronic hydrocephalus but is less so in cases of acute increases in intracranial pressure. The dura mater is poorly compliant and does not accommodate increases in intracranial pressure. Infants, despite open fontanels, remain at risk for herniation syndromes during acute elevations in intracranial pressure (e.g., traumatic brain injury, meningitis, acute hydrocephalus).

Infants are at great risk for hypothermia due to poor abilities in preventing and responding to heat loss.

Thermoregulatory mechanisms in infants are immature and inefficient when responding to heat loss. A variety of peripheral tissues provide afferent input to the temperature regulating hypothalamus. The hypothalamus supplies efferent output to effector organs that provide thermogenesis. Infants have less

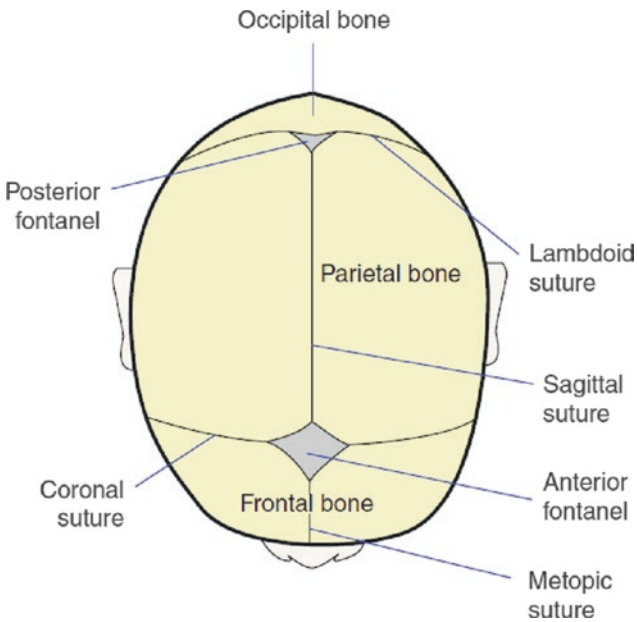


Fig. 47.3 Sutures and fontanels present in the infant skull

effective efferent mechanisms to produce heat. In particular, they have a limited or absent ability to shiver. The ability of infants to prevent heat loss is also limited. Their large surface area to volume ratio provides a greater area for heat loss and they lack significant amounts of body fat for insulation. Since infants have a limited ability to maintain heat and respond to heat loss poorly, close attention to maintaining euthermia should be an essential component in the care of the sick infant.

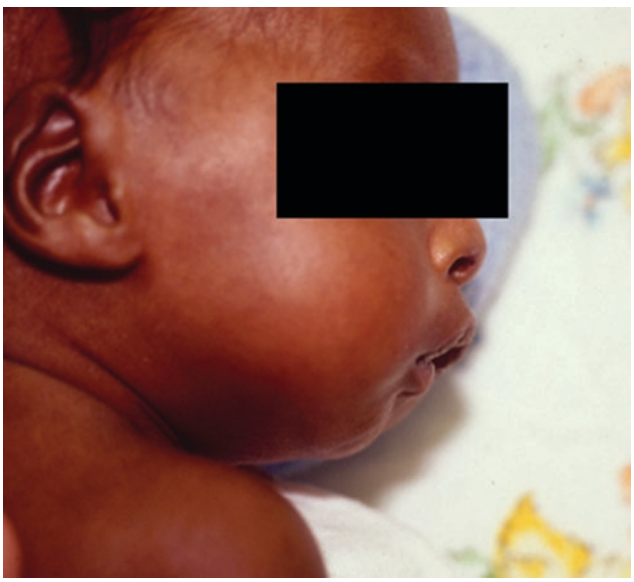
47.3 Initial Management of the Infant Presenting with Life-Threatening Critical Illness

Stabilization should proceed in a systematic manner adhering to the "ABCDs" as outlined in the Pediatric Advanced Life Support approach. Following an expanded ABCD format can aid in stabilization and early initiation of lifesaving therapies in the infant presenting in extremis. When faced with any critically ill infant, a basic tenet is to assume overwhelming infection and administer antibiotics rapidly after blood cultures have been obtained.

47.3.1 Airway

As previously discussed, the airway of a small infant is higher, is anterior, and has more compliant supraglottic tissue than that of an older child. As a result, they are at greater risk for upper airway obstruction. It is important to note the presence or absence of airway protective reflexes and appreciate anatomic features that may predispose a difficult intubation (e.g., micrognathia or retrognathia, ◘ Fig. 47.4). Proper positioning of the infant during airway management is essential due to the aforementioned factors that predispose airway obstruction. Often, improperly placed padding leads to hyperflexion or hyperextension resulting in misalignment of the oral, pharyngeal, and tracheal axes. A neutral sniffing position that aligns the oral, pharyngeal, and tracheal axes is best achieved by inserting a thin towel under the shoulders to offset the infant's prominent occiput (◘ Fig. 47.1). An appropriately sized endotracheal tube should be chosen

Achieving a neutral sniffing position in an infant may require placement of a thin pad below the lower neck and shoulders to offset the prominent occiput.



◘ **Fig. 47.4** Infant with history of difficult intubation following respiratory arrest from bronchiolitis and aspiration. Findings of retro/micrognathia and submucosal cleft are consistent with the Pierre Robin sequence

according to an estimated weight. A 3.0 mm endotracheal tube inserted to a depth of 9 cm is appropriate for a small (less than 3.0 kg) infant, and a 3.5 mm endotracheal tube inserted to a depth of 11 cm is appropriate for infants up to 7 kg.

47.3.2 Breathing

The examiner should quickly assess ventilation and oxygenation. The rate, depth, work of breathing, and oxyhemoglobin saturation should be noted. An arterial blood gas should be obtained if there is any question of inadequate gas exchange. If there is evidence of hypoxemia or severe respiratory acidosis, bag mask ventilation with 100% oxygen should be initiated while preparing for endotracheal intubation. If there is coexisting hemodynamic compromise, volume expansion prior to the institution of positive pressure ventilation may be necessary to prevent hypotension.

47.3.3 Circulation

Pulse rate, rhythm, quality of distal perfusion, mental status, and urine output should be assessed. If necessary, begin volume resuscitation with 20 mL/kg boluses of normal saline and reassess clinically for signs of fluid overload before initiating subsequent fluid boluses. In an infant less than 4–8 weeks of age with poor to absent distal pulses, gallop rhythm, enlarged liver, abnormal chest radiograph, and acidosis, consider the presence of an undiagnosed congenital heart defect or myocarditis.

A high index of suspicion for left-sided obstructive congenital heart disease should be maintained in all infants less than 30 days of age presenting in circulatory failure.

Left-sided heart lesions with ductal dependent systemic blood flow (e.g., coarctation of the aorta, critical aortic stenosis, hypoplastic left heart syndrome) can present following discharge from the hospital. This contrasts with right-sided lesions with ductal dependent pulmonary blood flow (e.g., pulmonary stenosis/atresia, tricuspid atresia) that often present shortly after birth with cyanosis as the primary abnormality. Prostaglandin E_1 (0.05–0.1 mcg/kg/min) should be instituted early in consultation with a pediatric cardiologist when obstructive left-sided lesions are suspected. Continuous cardiopulmonary monitoring is essential during prostaglandin infusion as apnea is a known side effect.

A rapid (>220 bpm), regular, narrow complex tachycardia is suggestive of supraventricular tachycardia. P waves may be inverted, retrograde, or absent. In infants who are hemodynamically stable with adequate distal perfusion, vagal maneuvers (e.g., ice water in a plastic bag forcefully applied to face without obstructing ventilation) may be attempted. Adenosine should be administered if vagal maneuvers fail. In hemodynamically unstable infants with poor perfusion, rapid administration of adenosine (0.1 mg/kg) or synchronized cardioversion (0.5–1 J/kg) is indicated.

47.3.4 Establishing Vascular Access

47.3.4.1 Peripheral Access

Early securement of venous access is a critical procedure but may be challenging in a small infant. Peripheral venous access sites include the following: upper extremities (cephalic, basilic, and median cubital veins in the forearm and the dorsal veins of the hand), lower extremities (great saphenous vein at the ankle

and dorsal arch veins of the dorsal foot surface), scalp, and external jugular vein. Reliable peripheral venous access will allow for quick initiation of isotonic fluid resuscitation and drug delivery. Complications of peripheral venous access are rare but include phlebitis, hematoma, cellulitis, osteomyelitis, infiltration, and skin sloughing. If peripheral venous access cannot be obtained rapidly (within the first 2–5 min) in a critically ill infant with progressive decompensation, an interosseous (IO) needle should be placed.

47.3.4.2 Interosseous Access

Intraosseous access via manual needles or battery-powered IO drivers allows direct access to the medullary bone marrow and the venous drainage system of long bones. Within the metaphysis (between growth plate and shaft, diaphysis) of long bones, an extensive system of intramedullary blood vessels can be accessed with the placement of an IO needle.

Sites for emergent IO access include the following: proximal tibia, distal femur, distal tibia/medial malleolus, proximal humerus, manubrium/upper sternum, anterior inferior iliac spine, clavicle, and distal radius. IV medications and fluids can be administered by the IO route. Colloids, crystalloids, blood products, antibiotics, epinephrine, dopamine, dobutamine, norepinephrine, lidocaine, atropine, and sodium bicarbonate can all be given via IO access. Additionally, basic diagnostic studies can be obtained from IO access blood samples: glucose, hemoglobin, pH, pCO_2, serum bicarbonate, sodium, chloride blood urea nitrogen, creatinine, serum drug levels, and blood cultures (e.g., bacterial, viral, or fungal cultures). Bone marrow values for the certain studies may not be accurate, so interpretation of these labs should be done with caution and include blood oxygenation, white blood cell count, potassium, aspartate aminotransferase, alanine aminotransferase, and ionized calcium.

Contraindications to IO placement include fractured bone, overlying trauma, and prior IO attempt. Relative contraindications include infection at the insertion site, burns, and bone fragility (e.g., osteogenesis imperfecta). Presence of a right to left intracardiac shunt (e.g., tetralogy of Fallot, pulmonary atresia) is also a relative contraindication due to the risk of cerebral embolus from bone marrow fat.

Intraosseous cannulation needles should be removed as soon as peripheral or central venous access is obtained to avoid complications. Rare complications of IO access include bone fractures at the site of insertion, infusion of fluids into the subcutaneous space causing compartment syndrome, infiltration of medications into the subcutaneous space, infection, osteomyelitis, pain on use, dislodgement, and fat embolism.

47.3.4.3 Central Venous Access

Establishing central venous access may be required to facilitate cardiovascular support and pressure monitoring. Central access sites in the critically ill infant include the umbilical vein, femoral vein, internal jugular vein, and subclavian vein. For newborns less than 10 days of age, the umbilical vein can be accessed emergently. The umbilical vein generally remains patent 10–14 days after birth. Consider the following umbilical vein catheter (UVC) size based upon the infant's weight: less than 1.5 kg, 3.5 French catheter; 1.5–3.5 kg, 5 French catheter; and greater than 3.5 kg, 8 French catheter. A UVC should be passed through the ductus venosus so that its tip lies in the IVC above the diaphragm or at the juncture of the IVC with the low right atrium. UVC placement is contraindicated in neonates with any abdominal wall abnormalities such as

gastroschisis, omphalocele, peritonitis, portal venous hypertension, necrotizing enterocolitis, or omphalitis.

The internal jugular and femoral vein can be cannulated using an ultrasound-guided Seldinger technique. As a general guide, consider using a 3 or 4 French catheter based on size of the vessel and infant. Catheter tip positioning should be at the superior vena cava–right atrium junction for the internal jugular and subclavian lines. Femoral lines are positioned within the inferior vena cava. To accurately determine the appropriate length of the central line catheter, it is essential to measure from the point of insertion to the expected placement position on each patient. After placement of a central venous catheter, line confirmation should be done via radiograph, venous blood gas analysis, and transduction of the line for waveform analysis.

Complications related to insertion of central venous lines include arterial puncture, guidewire fracture, hematoma, hemorrhage, air embolism, and arrhythmias. Subclavian and internal jugular vein complications also include hemothorax and pneumothorax. Post catheter insertion complications are mainly related to infection and thrombosis.

47.3.5 3 Ds

47.3.5.1 Disability

Infants with suspected meningitis, intracranial injury, or certain metabolic disorders may have progressive increased intracranial pressure. Serial neurologic assessment should be performed monitoring for signs of raised intracranial pressure (altered mental status, hypertension, bradycardia, bulging fontanel) or occult seizure activity. Raised intracranial pressure should be treated with maintenance of oxygenation and mean arterial pressure, elevation of the head of bed to 30 degrees to promote jugular venous drainage, and 3% NaCl or mannitol 0.5–1 g/kg. Hyperventilation should be reserved for impending herniation.

47.3.5.2 Dextrose

All critically ill infants require a rapid bedside glucose determination within minutes of arrival.

Without exception, every critically ill infant should have a rapid glucose determination performed within minutes of arrival. Inadequate intake, limited glycogen stores, and an increase in glucose utilization during stress states can lead to clinically significant hypoglycemia. A primary endocrine or metabolic abnormality (congenital adrenal hyperplasia, fatty acid oxidation disorders) may also lead to hypoglycemia. Hypoglycemia should be treated with 0.5–1 g/kg of dextrose (5–10 mL/kg of D_{10}, 2–4 mL/kg of $D_{25,}$ or 1–2 mL/kg D_{50}).

47.3.5.3 Drugs

It is important to inquire about medications given to the infant and those taken by a breast-feeding mother. Also, consider specific medications the infant requires for further stabilization (e.g., antibiotics, acyclovir, intubation medications, prostaglandin, inotropes, or pressors).

47.3.5.4 Euthermia/Equipment

Due to their relatively large surface area, reduced subcutaneous fat stores, and immature thermoregulatory mechanisms, small infants are at risk for significant heat loss. Hypothermia leads to increased oxygen consumption and pulmonary and systemic vasoconstriction and impedes effective resuscitation. The infant is best kept warm by utilizing a radiant warmer. Alternatively, warmed blankets can be used.

An important caveat exists in the infant with suspected neurologic injury. Active cooling for suspected neurologic injury (except for its use in perinatal hypoxic ischemic encephalopathy) is currently unproven. However, infants with suspected neurologic injury should not be rapidly rewarmed and hyperthermia should be avoided.

Equipment must be checked for proper functioning. An acute decompensation during stabilization may be from equipment failure rather from a true physiologic change.

47.3.5.5 Foley

A bladder catheter is necessary to assess urinary output during volume resuscitation.

47.3.5.6 Gastric Tube

If the airway is secured, insert a gastric tube to decompress the stomach. This is especially important if prolonged bag mask ventilation occurred prior to intubation.

47.3.5.7 Hemoglobin/Hydrocortisone

Consider the need for packed red blood cell transfusion in infants with ongoing blood loss or the need for surgery. Consider the need for steroid replacement in an infant with suspected adrenal insufficiency. Suspect adrenal insufficiency in any infant with fluid and pressor refractory shock.

47.3.6 Initial Investigations

During stabilization, initial data gathering should occur. A rapid beside glucose determination is essential and should be performed as soon as possible. Blood and urine cultures, a complete blood cell count with differential, electrolytes, liver function tests, a coagulation profile, and urinalysis should be obtained in all critically ill-appearing infants. Culture and rapid antigen testing for viral pathogens should be obtained if a viral infection is clinically suspected.

Arterial blood gas determination will aid in the assessment of gas exchange and acid–base status. When performed after hyperoxygenation, evaluation of the PaO_2 may help differentiate a primary pulmonary process versus congenital heart disease with restriction of pulmonary blood flow (after 100% O_2 for 10 min, pulmonary process, $PaO_2 > 150$; congenital heart disease, $PaO_2 < 50$). A methemoglobin and carboxyhemoglobin level should be obtained in infants with unexplained cyanosis.

A methemoglobin and carboxyhemoglobin level should be obtained in infants with unexplained cyanosis.

If an inborn error of metabolism is suspected, blood for lactate, pyruvate, ammonia, and amino acids should be obtained as well as urine for amino and organic acids. Cortisol and 17-hydroxyprogesterone levels should be obtained in infants suspected to have congenital adrenal hyperplasia. Blood and urine for toxicological testing are warranted if accidental or intentional ingestion is suspected.

A lumbar puncture is best deferred until the infant is stable. The lack of cerebrospinal fluid for analysis does not preclude early initiation of antibiotics or antiviral agents.

Imaging studies including chest/abdominal radiographs, head computerized axial tomography, skeletal survey, and echocardiogram should be obtained as clinical suspicion dictates.

Lumbar puncture may place the critically ill infant at undue risk and should be deferred until gas exchange and hemodynamics are stabilized and intracranial hypertension is ruled out.

47.4 Differential Diagnosis and Specific Diagnostic Considerations

The presentation of the critically ill infant is dependent upon the previous health of the infant, the primary organ system affected, and when in the course of the illness the infant is brought to medical attention. Often, in the presence of severe disease, the infant may present with derangements in respiratory, cardiovascular, or neurological function. A meticulous and ordered examination can quickly narrow the diagnostic possibilities (Table 47.1) and allow the timely initiation of specific therapies (i.e., prostaglandin for ductal-dependent congenital heart disease).

Table 47.1 Differential Diagnosis of the Critically Ill-Appearing Infant Based on History and Examination Findings

Organ System	Examination	Diagnoses
General appearance	Cyanosis	CHD, respiratory failure, methemoglobinemia, sepsis
	Hypotonia	Botulism, sepsis, SMA, IEM
	Dehydration/ emesis	Gastroenteritis, pyloric stenosis, malrotation with volvulus, Congenital adrenal hyperplasia
HEENT	Bulging fontanel	Meningitis, AHT, IEM
	Retinal hem.	AHT
	Ptosis/mydriasis	Botulism
	Miosis	Toxic ingestion
Cardiovascular	Tachycardia	Hypovolemia, sepsis, tachyarrhythmia, myocarditis, toxic Ingestion
	Bradycardia	IICP (meningitis, AHT)
	Poor perfusion	Hypovolemia, sepsis, CHD, tachyarrhythmia, myocarditis
Respiratory	Apnea	RSV bronchiolitis, sepsis, IICP
	Wheeze/crackles	Bronchiolitis, airway anomaly, CHD, myocarditis
Gastrointestinal	Distention/tender	Hirschsprung's enterocolitis, volvulus, NEC
	Mass	Pyloric stenosis, intussusception
	Hepatomegaly	CHD, myocarditis, IEM
Skin	Vesicles	Herpes simplex
	Purpura	Sepsis, inflicted trauma
	Petechiae	Sepsis, thrombocytopenia
Neurologic	Irritability/ lethargy	Meningitis, AHT, IEM
	Bulbar findings	Botulism, IICP

CHD congenital heart disease, *SMA* spinal muscular atrophy, *AHT* abusive head trauma, *IEM* inborn error of metabolism, *IICP* increased intracranial pressure, *NEC* necrotizing enterocolitis, *RSV* respiratory syncytial virus

47.5 Specific Diagnostic Considerations

47.5.1 Infectious

47.5.1.1 Neonatal Sepsis (Sepsis Neonatorum)

Due to the potential of acquiring pathogens from the maternal birth canal and a relative immunocompromised state, the newborn infant is at particular risk for overwhelming infection. The incidence of neonatal sepsis ranges from 1 to 10 per 1000 live births. Important etiologic agents are summarized in ◘ Table 47.2.

Early-onset disease is transmitted vertically (intrauterine or acquisition during delivery) and is often characterized by multisystem disease. Late-onset disease can be acquired vertically or horizontally from the environment and may be focal (e.g., meningitis, pneumonia) or have severe systemic involvement.

The neonate's immunocompromised state and potential for acquisition of serious pathogens from the birth canal create a significant risk for overwhelming infection.

Two pathogens of particular importance to the pediatric intensivist are group B streptococcus and herpes simplex virus. Respiratory syncytial viral infection is a common cause of severe illness in infancy and is discussed in detail in ▶ Chap. 33.

47.5.1.2 Group B Streptococcal Disease (GBSD)

Group B streptococcus (*Streptococcus agalactiae*) is a facultative gram-positive diplococcus that has polysaccharide capsule and deacylated glycerol teichoic acids as major virulence factors. GBSD is a major cause of systemic and focal infections in infants and accounts for 70% of all early-onset sepsis. Approximately 5–35% of all pregnant women are colonized with GBS. Although up to half of colonized women will transmit GBS to their infants, only 1–2%

◘ **Table 47.2** Etiologic agents of neonatal sepsis and typical time of presentation

Organism	Early onset (birth, 6 days)	Late onset (>7 days)
Gram-positive bacteria		
Group B streptococcus	+ + +	++
Listeria monocytogenes	+	+
Enterococci	+	+
Staphylococcus aureus	+	+
Coagulase-negative staph.	+	
Streptococcus pneumoniae		+
Gram-negative bacteria		
Escherichia coli	+ +	++
Other gram-negative enteric	+	+
Haemophilus influenzae		+
Viruses		
Cytomegalovirus	+ +	+
Herpes simplex	+	+ +
Enteroviruses	+	+ +
Respiratory syncytial virus	+	+ +

of colonized infants will become symptomatic. With the development of widespread maternal chemoprophylaxis, the incidence of GBSD has fallen from 2/1000 live births to 0.6/1000 live births. The incidence of late-onset disease has remained stable at 0.4/1000 live births.

Clinical Manifestations

Early-onset GBS disease often presents shortly after birth and may resemble hyaline membrane disease.

Early-onset disease – Early-onset disease usually occurs within the first 24 h of life (range 0–6 days) and accounts for 75% of GBSD. A history of maternal perinatal complications is often present such as prolonged rupture of membranes, premature birth, or chorioamnionitis. Early-onset disease may present as fulminant sepsis, pneumonia, or occasionally meningitis. Pulmonary disease often mimics hyaline membrane disease and may be further complicated by severe pulmonary hypertension.

Unlike early-onset GBS disease, late-onset disease often presents with focal infections such as meningitis and bone and soft tissue infections.

Late-onset disease – Late-onset disease occurs at approximately 2–4 weeks of age (range, 7 days–3 months). The infant with late-onset disease often presents with fever and is subsequently found to have bacteremia. Meningitis accounts for 25% of late-onset disease. Focal infections such as septic arthritis, osteomyelitis, adenitis, and cellulitis are seen in 20% of cases. In contrast to early-onset disease, infants presenting with late-onset disease often lack multisystem involvement. The case fatality rate of late-onset disease is 2.8% versus 4.7% for early-onset disease.

In addition to late-onset GBSD, *Escherichia coli*, *Listeria monocytogenes*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, and, to a much lesser extent, *Haemophilus influenzae* type b can cause sepsis in infants.

The workup for an infant presenting with signs and symptoms of sepsis includes:

1. Blood culture
2. Urinalysis and urine culture
3. Lumbar puncture if the infant is clinically stable
4. Cultures from potential sources (e.g., tracheal aspirate if intubated, purulent eye drainage, or skin pustules)
5. Complete blood count with differential and platelet count
6. Chest radiograph if there are respiratory symptoms
7. Serum lactate
8. Inflammatory markers (e.g., C-reactive protein and/or procalcitonin levels)

Treatment

Initial treatment of a neonate less than 7 days of age with suspected septicemia includes ampicillin for GBS and *Listeria monocytogenes* coverage and an aminoglycoside (gentamicin) to cover *E. coli* and other gram-negative organisms. In infants older than 7 days, a third-generation cephalosporin such as cefotaxime can be used in place of an aminoglycoside. When meningitis is suspected in the infant older than 7 days, vancomycin should be used in place of (or in addition to) ampicillin to cover *S. pneumoniae* (◘ Table 47.3). Antibiotic coverage can be narrowed to penicillin G only after definitive GBS identification and sensitivity testing.

Infants older than 7 days with a maternal history of herpes, abnormal CSF findings, and/or progressive sepsis should receive IV acyclovir in addition to antibiotics pending definitive identification of a causative organism.

47.5.1.3 Herpes Simplex Virus

Neonatal herpes simplex virus (HSV) is among the most devastating neonatal pathogens. Most infants are infected at the time of delivery and become symptomatic between 7 and 16 days of life. Rarely, in-utero transmission occurs (5%) and the infant is symptomatic at birth with hyperpigmentation or

Table 47.3 Empiric antibiotic treatment of infants with presumed sepsis or meningitis

Empiric treatment of suspected early-onset infant infections (less than 7 days of age)	
Bacteremia/ sepsis/ pneumonia	Ampicillin *PLUS* gentamicin
Meningitis	Ampicillin
	PLUS
	Gentamicin *OR* cefotaxime
Empiric treatment of suspected late-onset infant infections (greater than 7 days)	
Bacteremia/ sepsis/ pneumonia	Ampicillin OR vancomycin
	PLUS
	Gentamicin *OR* cefotaxime
Meningitis	Ampicillin *AND/OR* vancomycin
	PLUS
	Gentamicin *OR* cefotaxime Add acyclovir in infants less than 4 weeks of age with ill appearance, mucocutaneous vesicles, seizures, or cerebrospinal fluid (CSF) pleocytosis and in older infants with clinical findings of HSV infection

hypopigmentation, cutaneous scarring or rash, CNS abnormalities including intracranial calcifications microcephaly or encephalomalacia, and ocular anomalies including microphthalmia, optic atrophy, or chorioretinitis.

Vertically acquired HSV type 2 infections account for 90% of neonatal herpes infections. Horizontally acquired HSV type 1 infections from close contacts with fever blisters, whitlow, or other skin infections account for the remainder of neonatal HSV disease. Maternal primary infection during delivery leads to a high infant attack rate (33–50%). Only 25% of women with a primary infection are symptomatic at delivery, thus making it difficult to consistently implement preventative strategies. In contrast, recurrent HSV infection at delivery carries only a 1–2% attack rate.

Neonatal herpes presents in three forms: disseminated disease, localized CNS disease, and disease localized to the skin/eye/mucosa. The characteristics of each type are summarized in Table 47.4. Overlap between these types is known to occur.

The diagnosis of neonatal HSV infection should be considered in any septic-appearing infant less than 4 weeks of age regardless of the presence of cutaneous lesions. It is imperative that the intensivist maintains a high index of suspicion for HSV infection as early treatment can significantly reduce morbidity.

Maternal primary HSV infection has an attack rate as high as 50%.

Neonatal HSV infection is confirmed by isolation of virus in tissue culture from lesions, mucosa, and cerebrospinal fluid. Use of antigen identification techniques such as enzyme-linked immunosorbent assay and direct fluorescent antibody testing are also diagnostic. Polymerase chain reaction testing has become the most commonly used technique for the rapid detection of HSV in cerebrospinal fluid.

Absence of skin lesions does not preclude life-threatening neonatal HSV infection.

Acyclovir is the antiviral of choice in the treatment of neonatal HSV. Disseminated and CNS disease requires parenteral acyclovir at 60 mg/kg/day in three divided doses for 21 days. Disease of the skin/eyes/mucosa requires

Table 47.4 Summary of neonatal HSV infection

Type	Manifestations	Absence of skin lesions (%)	Mortality (%)
Disseminated	Vesicles	39	31
	Lethargy		
	Fever		
	DIC		
	Pneumonia		
Localized CNS	Vesicles	32	6
	Lethargy		
	Seizure		
Localized skin/eyes/mucosa	Vesicles	17	<1
	Keratoconjunctivitis		
	Fever		

DIC disseminated intravascular coagulation

14 days of treatment at the same dose with concomitant ophthalmic antiviral therapy. Early institution of acyclovir reduces mortality by 50% and substantially reduces morbidity. Aggressive supportive therapy including treatment of respiratory failure, shock, seizures, and coagulopathy is often necessary.

47.5.2 Cardiac

47.5.2.1 Congenital Heart Disease

The following is an overview of the presentation and management of the small infant with heart disease. Specific discussions of congenital and acquired heart disease are found elsewhere in the text. Infants with congenital heart disease (CHD) may present with subtle symptoms such as poor feeding, failure to thrive, or irritability. Alternatively, they may present with obvious cyanosis, circulatory shock, and signs of congestive heart failure. The various presentations of CHD are dependent on several factors:

- The stage of cardiovascular transition
- Location of the lesion (right- vs. left-sided)
- Severity of the lesion (e.g., the degree of outflow obstruction, intracardiac shunting, myocardial compromise)

Two important milestones during the transition from neonatal to postnatal circulation that may "unmask" CHD are the closure of the ductus arteriosus (2 days–3 weeks) and the progressive decline in pulmonary vascular resistance (birth–18 weeks).

Clinical manifestations of CHD can vary dramatically based upon the above factors. Presentations of severe CHD may be simplified as:

Right-sided CHD usually presents shortly after birth with cyanosis.

- *The cyanotic infant* (right-sided lesions with right to left shunting)
- *The infant in cardiogenic shock* (left-sided lesions with obstruction)
- *The infant in congestive heart failure* (lesions producing large left to right shunts)

The Cyanotic Infant

Lesions in which pulmonary blood flow are ductal-dependent (severe tetralogy of Fallot, pulmonary stenosis/atresia, tricuspid atresia with restrictive VSD, transposition of the great arteries) often present in the first few hours after birth. Clinically, these lesions are characterized by:

- Minimal respiratory distress
- Fair to good distal perfusion
- Presence or absence of murmur
- Failed hyperoxia test (no significant increase in PaO_2 on 100% FiO_2)
- Abnormal chest radiograph (decreased pulmonary vascular markings, abnormal cardiac contour)
- Minimal metabolic acidosis

The treatment of cyanotic CHD is definitive repair (e.g., arterial switch for transposition of the great arteries) or an initial palliative surgery (e.g., systemic to pulmonary shunt for severe right ventricular outflow obstruction). The preoperative management includes restoration of pulmonary blood flow via the ductus arteriosus with the institution of prostaglandin E_1 (PGE_1). Due to the propensity of prostaglandin to induce apnea and its potent vasoactive effects, careful ongoing attention to respiratory function and hemodynamics is essential.

Left-sided obstructive CHD may present acutely, days to weeks after birth, with cardiogenic shock.

The Infant in Cardiogenic Shock

Lesions producing obstruction to systemic blood flow include coarctation of the aorta, interrupted aortic arch, critical aortic stenosis, and hypoplastic left heart syndrome (HLHS). These lesions increase in severity and become clinically apparent with closure of the ductus arteriosus. As such, infants may present after newborn discharge with acute onset of cardiogenic shock. The closure of the ductus arteriosus in infants with HLHS may be catastrophic if intracardiac left to right shunting is restricted. The closure of the ductus arteriosus in severe coarctation of the aorta may also cause profound circulatory shock as pulmonary to systemic blood flow is eliminated. Additionally, systemic blood flow is further compromised as constriction of ectopic ductal tissue in the aorta increases the severity of the coarctation. Obstructive left-sided lesions often present with signs of cardiogenic shock:

- Poor distal perfusion
- Ashen to mildly cyanotic coloration
- Respiratory distress
- Severe metabolic acidosis
- +/– hepatomegaly
- +/– murmur
- Chest radiograph with pulmonary venous congestion and cardiomegaly

The diagnosis of a left-sided obstructive lesion producing cardiogenic shock requires a high index of suspicion in infants less than 2 months of age who present in extremis.

The initial management of these infants often requires cardiopulmonary resuscitation. The early use of PGE_1 to reestablish systemic blood flow and emergent pediatric cardiology consultation may be lifesaving. In addition to PGE_1, an emergent atrial septectomy may be required in infants with inadequate interatrial communication. Atrial septectomy or balloon septostomy allows decompression of the left atrium and flow of oxygenated pulmonary venous return across the atrial septum. Infusions of inotropes such as epinephrine and dobutamine are often required for myocardial support. Sepsis, myocarditis, and abusive head trauma can also produce profound circulatory dysfunction that mimic those seen in CHD with obstruction to systemic flow.

The early use of PGE_1 to reestablish systemic blood flow, may be lifesaving in infants with left-sided obstructive lesions such as HLHS and coarctation of the aorta.

Once systemic blood flow is reestablished, preoperative balancing of the pulmonary and systemic circulations is required. For infants with HLHS on prostaglandin, avoidance of pulmonary overcirculation and decreasing systemic circulation can be achieved by maintaining arterial oxygen saturations between 70% and 80% (Qp:Qs = 1:1). Strategies to achieve this balance include avoiding the use of supplemental oxygen, tolerating hypercarbia ($PaCO_2$ 45–50 mm Hg), maintaining the hematocrit between 40% and 45%, and rarely, the addition of hypoxic gas mixtures to further decrease pulmonary blood flow. Further manipulation of pulmonary and systemic vascular resistances is individualized based on the infant's hemodynamic profile.

CHD producing large left to right shunts presents more indolently with signs and symptoms of congestive heart failure.

The surgical correction may include the definitive repair of the obstructive lesion (e.g., coarctation of the aorta) or, alternatively, a staged repair beginning with a neonatal palliative procedure (i.e., Norwood procedure for HLHS).

The Infant with Congestive Heart Failure (CHF)

Lesions in which the natural fall in pulmonary vascular resistance causes pulmonary overcirculation include truncus arteriosus (presenting earliest), ventricular septal defects, endocardial cushion defects, and patent ductus arteriosus. The presentation may be delayed and indolent as signs and symptoms of pulmonary overcirculation are progressive. Infants with significant left to right shunts may present with:

- Subtle complaints (failure to thrive, poor feeding, diaphoresis)
- Moderate respiratory distress
- Hyperdynamic precordium usually with murmur
- Hepatomegaly
- Chest radiograph with cardiomegaly and increased pulmonary vascular markings
- Right ventricular hypertrophy on electrocardiogram

Pending definitive surgical correction, the management of infants with large left to right shunts centers around "anti-congestive" measures. These interventions include the use of diuretics, afterload-reducing agents, and, at times, inotropes. Depending upon the degree of left to right shunting, anti-congestive regiments are individualized. Rarely, a palliative procedure (i.e., pulmonary artery banding) is required until definitive repair can be achieved.

47.5.3 Neurologic

47.5.3.1 Infantile Botulism

Clostridium botulinum is a group of gram-positive, rod-shaped, spore-forming, obligate anaerobic bacteria. Infantile botulism usually occurs in infants less than 1 year of age. The ingestion of *Clostridium botulinum* spores, via contaminated foods or more commonly from soil, leads to intestinal colonization. The spores of *C. Botulinum* are heat resistant, surviving up to 100 °C, but they can be destroyed by heating to 120 °C for at least 5 min. Infants, particularly those who are breast-fed, appear more susceptible to *C. botulinum* intestinal invasion due to a lack of competing microbial flora and immature host defenses. Replication within the intestines leads to production of a potent neurotoxin. After invasion into the circulation, the neurotoxin acts presynaptically on cranial and peripheral nerves to inhibit the release of acetylcholine.

The initial symptom is often constipation, followed by signs of a descending paralysis beginning with the cranial nerves. Bulbar findings include a weak

cry, poor suck, inactivity, and bilateral ptosis. The loss of airway reflexes coupled with progressive muscular hypotonia often results in respiratory failure. Electromyography findings are not pathognomonic and may not be present in the early disease state. Nevertheless, certain EMG findings which may support the diagnosis of botulism include brief duration, small amplitude, and overly abundant motor potentials (BSAPS). The definitive diagnosis is made by the isolation of C. *botulinum* from the stool. This may be exceedingly difficult due to constipation and may be aided by the administration of a non-bacteriostatic fluid enema.

Treatment remains mainly supportive with careful attention to fluids, electrolytes, and enteral nutrition. Prolonged mechanical ventilation may be required. Human-derived botulism immune globulin, when started early in the course, has been found to significantly reduce the duration of hospitalization from 5.7 to 2.6 weeks. Drugs known to impede neuromuscular transmission (i.e., aminoglycosides) should be avoided.

C. botulinum produces a neurotoxin that acts presynaptically on cranial and peripheral nerves to inhibit the release of acetylcholine.

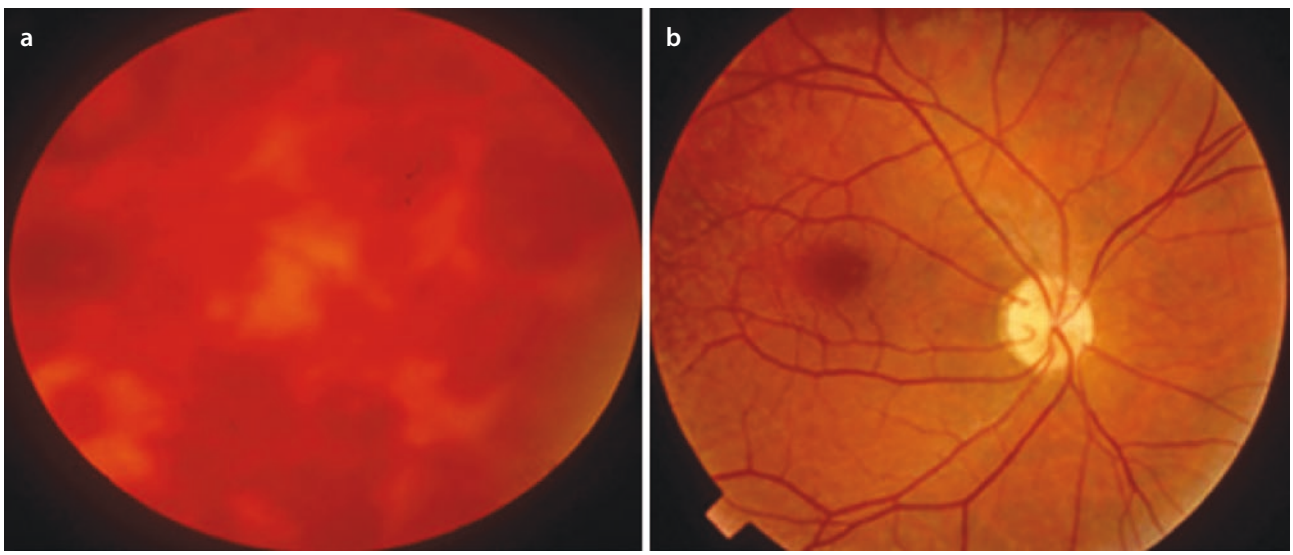
Infantile botulism is characterized by bulbar symptoms followed by a descending paralysis.

47.5.3.2 Abusive Head Trauma in Infancy

Abusive head trauma (AHT) is the leading cause of life-threatening brain injury in infants. Ninety-five percent of all intracranial injuries occurring in children less than 1 year of age are secondary to abuse, particularly violent shaking. The prognosis for infants suffering AHT is often dismal; 25% die and the remainder will have a significant degree of neurological impairment.

In 1946, John Caffey first described long bone fractures and chronic subdural hematomas in infants without an apparent history of trauma. He later described the classic triad seen in shaken infants: retinal hemorrhages (◘ Fig. 47.5), subdural hematomas, and little, if any, signs of external trauma. The intracranial and retinal findings are due to repetitive acceleration and deceleration that occur during shaking. Rotational forces during shaking cause the brain to turn on its central axis further exacerbating brain injury. Impact with a surface, against which the infant is thrown, contributes to the deceleration injury.

An infant who has been shaken can present with subtle symptoms such as irritability and vomiting. Alternatively, the intensivist may be faced with an



◘ **Fig. 47.5** **a** Severe retinal hemorrhaging in an infant after violent shaking. **b** Comparison of normal retina from an uninjured infant

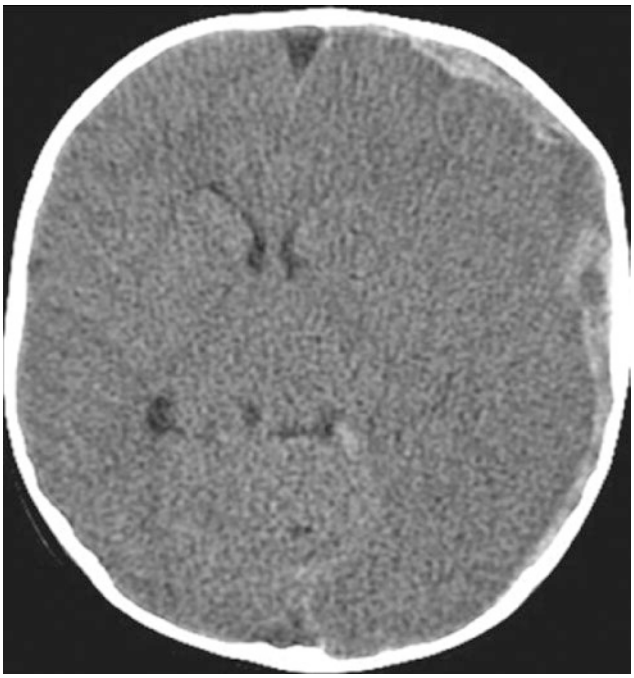


Fig. 47.6 Left subdural hematoma with severe edema and midline shift

infant with profound neurological dysfunction due to rising intracranial pressure. Neurological injury may consist of subdural hematomas (often interhemispheric), intracranial hemorrhage, axonal injury, and ischemic injury. Profound cerebral edema may occur soon after presentation (Fig. 47.6). Respiratory failure and hemodynamic compromise are usually concomitant in such cases. Secondary brain injury from hypoxia and ischemia contributes to poor outcomes. The initial management focuses on cardiopulmonary resuscitation and the management of intracranial hypertension. The prevention of secondary brain injury using cerebral protective strategies is detailed in ▶ Chap. 25 and in the *Guidelines for the Acute Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents*. Key components of these guidelines are summarized in ▶ Box 47.1.

The infant who has been violently shaken often presents in extremis with multiorgan dysfunction.

Management of traumatic brain injury due to abusive head trauma is based on neuroprotective strategies to avoid secondary brain injury.

Although open fontanels increase the compliance of the intracranial vault, their presence does not confer full protection against intracranial hypertension. Neurosurgical evacuation of large hematomas and placement of an external ventricular monitor and drain may be required. A decompressive craniotomy is reserved for refractory intracranial hypertension. The correction of any coagulopathy, the identification and treatment of other injuries (cervical spine injury, intra-abdominal injuries, and orthopedic injuries), and the careful documentation of non-CNS abusive injury are imperative (see ▶ Chap. 48).

Required investigations in infants with suspected AHT include neuroimaging, dilated fundoscopic examination by a pediatric ophthalmologist, and a full skeletal survey. CT of the brain is often the initial neuroimaging obtained as it can rapidly detect hematomas, brain edema, and skull fractures. MRI has become standard in the assessment of the infant with suspected AHT. MRI of the brain and cervical spine can identify small extra-axial hemorrhages, parenchymal contusions, cord contusions, diffuse axonal injury, spinal ligament injury, and posterior fossa abnormalities that may not be identified on CT. In addition, MRI with diffusion-weighted imaging may detect cerebral ischemia

and focal edema not initially apparent on CT. MRI can aid in delineation of acute from subacute or chronic injury.

Pupillary dilation is best deferred until intracranial hypertension and herniation risk have abated. A full skeletal survey to determine the presence of acute and old fractures (Figs. 47.7 and 47.8) should be obtained after the infant is stable. A "babygram" is insufficient in the documentation of skeletal injury and should be used only for a screen for obvious fractures.

The presence of open fontanels does not preclude the need for intracranial pressure monitoring or the evacuation of large hematomas in infants with severe traumatic brain injury.

Despite the high likelihood that an initial coagulopathy is secondary to the release of tissue factor by the injured brain, for medicolegal concerns, a full hematological workup should be performed. Likewise, metabolic studies to exclude inborn errors of metabolism that may mimic abusive head injury such as glutaric aciduria type I should be obtained. Photographs of any external injury should be taken on the first day for use in any future legal proceedings. Social services should be consulted immediately to aid in documentation of the history and for removal of other children from the home, if the environment is deemed unsafe. Lastly, throughout the workup, the role of the intensivist should be as an objective data collector who must consider the constellation of all the findings prior to arriving at the diagnosis of abuse.

Box 47.1 Overview of Cerebral Protective Strategies Used in the Management of Traumatic Brain Injury (TBI) Secondary to Abusive Heads Trauma

Cerebral Protective Strategies

- Maintain mean arterial pressure to maintain CPP appropriate for age
- Avoid hypoxia, hypercarbia, hyperthermia
- Elevate head of bed 30°
- Use of external ventricular drain for ICP and CPP monitoring and for CSF drainage in severe head injuries (GCS < 8)
- Provide sedation and analgesia as needed
- Use of neuromuscular blockade if ICP refractory
- Maintain serum osmolar gradient using mannitol and/or 3% saline
- For refractory increased ICP, consider moderate hypothermia (34 °C), moderate hyperventilation, barbiturate coma, and/or decompressive craniotomy
- Closely monitor for seizures and if present treat aggressively with antiepileptics

EVD external ventricular drain, *CSF* cerebrospinal fluid, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, *GCS* Glasgow coma score

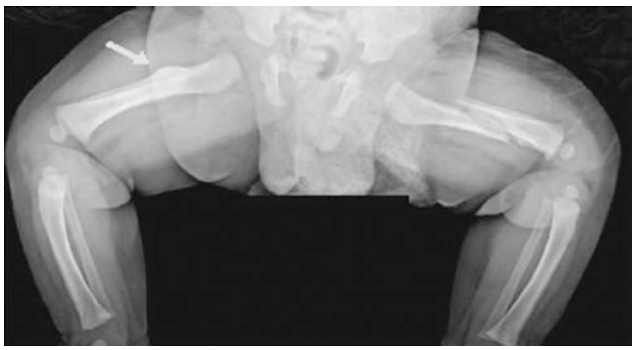


Fig. 47.7 Infant with acute midshaft femur fracture on left and old fracture on right as evidenced by callous formation (arrow)

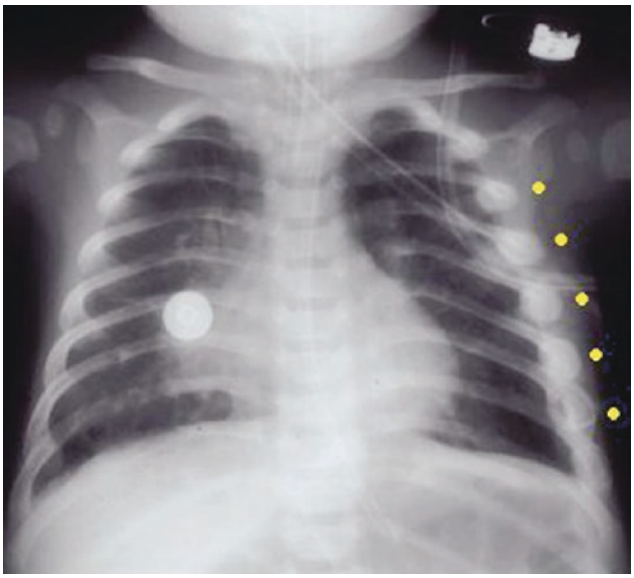


Fig. 47.8 Infant who required intubation due to sudden unexplained respiratory arrest. Multiple old rib fractures on the left (dots), old and new subdural hematomas, and retinal hemorrhages were consistent with abusive head trauma and non-accidental fractures

47.5.4 Hematologic

47.5.4.1 Methemoglobinemia

Methemoglobin has a low affinity for oxygen and causes normal hemoglobin to bind oxygen too avidly to allow release to distal tissues. This results in tissue hypoxia and acidosis.

Methemoglobin is produced when normal ferrous (2+) hemoglobin is oxidized to the ferric (3+) form. Methemoglobin creates a dual impediment to oxygen delivery. Of primary importance is methemoglobin's low affinity for O_2 that lowers the oxygen-carrying capacity of blood. Additionally, methemoglobin induces a left shift in the oxyhemoglobin dissociation curve. This shift causes the remaining ferrous hemoglobin to bind O_2 more avidly and impede release of O_2 to distal tissues. This combination leads to profound tissue hypoxia and acidosis.

Suspect methemoglobinemia in infants with a diarrheal prodrome that present with cyanosis and acidosis.

Methemoglobinemia can be congenital due to deficiencies in methemoglobin reduction enzymes or from abnormal hemoglobin structure (Hb M). More commonly, the disease is acquired due to an oxidant stress from an endogenous or exogenous source. Alteration in the gut flora during a diarrheal illness can lead to overproduction of nitrite which acts as an oxidant stress. Exogenous oxidant stressors include analgesics (e.g., benzocaine), aniline derivatives (e.g., dyes, inks, polishes), sulfonamides, dapsone, and nitrite−/nitrate-containing compounds (e.g., inhaled nitric oxide, well water, nitroprusside, nitroglycerin, bismuth subnitrate).

Clinical manifestations vary according to the percent methemoglobin present:

- 10–30% – Color change, fatigue, brown mucous membranes
- 30–50% – Cyanosis, dyspnea, tachycardia, dizziness, headache
- 50–70% – Worsening of above, profound acidosis, stupor, seizure
- >70% – Death

Suspicion of methemoglobinemia should arise when evaluating the cyanotic infant without obvious cardiac or respiratory pathology. Often the infant will appear more cyanotic than pulse oximetry would predict. Methemoglobin interferes with pulse oximetry by falsely absorbing light at 660 and 940 nm. Typical dual waveform bedside oximeters will give inaccurate readings of approximately 85%. Multiple wavelength co-oximetry, which measures the oxyhemoglobin saturation in the context of both reduced and abnormal hemo-

globins (e.g., methemoglobin, carboxyhemoglobin), provides a more accurate saturation. There is a minimal response of the SpO_2 to oxygen therapy and the blood may appear brown in color. Blood gas analysis reveals a higher than expected PaO_2, normal to low $PaCO_2$, and profound metabolic acidosis. An elevated methemoglobin level confirms the diagnosis.

If the methemoglobin level is greater than 30% or the infant is progressively symptomatic, methylene blue therapy should be initiated. Methylene blue (1–2 mg/kg of 1% solution) accelerates the alternate NADPH methemoglobin reductase pathway for the reduction of methemoglobin. When possible, a glucose-6-phosphate dehydrogenase (G6PD) screen should be performed prior to initiating therapy with methylene blue. Infants with G6PD have insufficient NADPH levels, and methylene blue may not be effective. Methylene blue may also induce hemolytic anemia in infants with G6PD deficiency. Ascorbic acid (300 mg po tid) is the treatment of choice in patients with G6PD deficiency.

Methylene blue accelerates the alternate NADPH methemoglobin reductase pathway for the reduction of methemoglobin. It should be considered for use if the methemoglobin level is greater than 30% or if the infant is progressively symptomatic.

47.5.4.2 Hemorrhagic Shock and Encephalopathy Syndrome

Hemorrhagic shock and encephalopathy syndrome (HSES), initially described in 1983, is a rare and devastating syndrome that affects infants generally under 1 year of age. HSES shares features with several conditions including heatstroke, sepsis, inborn errors of metabolism, hemolytic uremic syndrome, toxic ingestions, non-accidental trauma, and epilepsy. There is no pathognomonic test or clinical feature for HSES, and therefore, it is considered a diagnosis of exclusion. Using historical data, specific clinical criteria have been identified that aid in making the clinical diagnosis. These criteria include seizures, encephalopathy or coma, acidosis, severe shock, progressive disseminated intravascular coagulation, anemia, thrombocytopenia, elevated liver enzymes, and renal dysfunction. Hypoglycemia at presentation is also often seen. All cultures for bacterial or viral agents are negative for growth.

A single etiologic agent remains elusive as the cause of HSES. The cause is likely multifactorial including a genetic predisposition to the syndrome reminiscent of malignant hyperthermia.

HSES generally has a rapid onset with short prodrome. Infants typically present between the hours of 8 am and 11 am. A large diarrheal stool often heralds the onset of symptoms.

Trends in laboratory abnormalities may aid in establishing a diagnosis. Laboratory abnormalities reach their maximum level within 1–2 days of the onset of HSES and then slowly returned to normal. Infants have profound coagulopathy upon presentation. Hypoglycemia may be profound at the onset. Liver function tests are also abnormal and usually peak within 36 h of onset. Metabolic acidosis and elevated creatine kinase, blood urea nitrogen, and creatinine are seen early in the course but correct usually within 48 h. Rhabdomyolysis may be present and lead to severe pigment nephropathy and acute renal failure.

Neurological imaging may aid in the diagnosis of HSES, but findings are variable and include cerebral edema and petechial hemorrhages. The cerebral edema may range from mild to refractory. Head CT scan may be initially normal.

Broad-spectrum empiric antibiotics should be initiated early as the syndrome may closely resemble sepsis. HSES has a high mortality rate due its explosive presentation and multiple complications that may arise during its course. Survivors often have a significant degree of neurological sequelae. A small percentage of infants may have good outcomes if the shock and coagulopathy are not refractory.

47.5.4.3 Metabolic

A metabolic crisis is a rare but serious cause of severe physiologic derangements in infancy. A high index of suspicion for an inborn error of metabolism (IEM) should be maintained in all infants presenting critically ill without an obvious etiology. A positive family history of an IEM, sudden infant death, or consanguinity furthers suspicion for a metabolic disorder. The infant with an IEM may appear to have sepsis, a primary neurological disorder, or even cardiomyopathy at first glance but, indeed, may have a metabolic abnormality that requires prompt and aggressive treatment. A comprehensive discussion of IEM is found in ▶ Chap. 44. An overview of the initial workup and treatment of a critically ill infant with a suspected IEM is provided.

IEM in infancy may present with acute neurological or cardiac compromise or more indolently with poor feeding, tachypnea, temperature instability, and/or unusual odors.

Clinical Presentations

The clinical presentation is dependent upon the specific disorder; however, common presentations include:

- Lethargy progressing to encephalopathy
- Seizures
- Hypotonia/hypertonia
- Poor feeding history, recurrent vomiting, failure to thrive
- Apnea, tachypnea, or hyperpnea without obvious pulmonary pathology
- Temperature instability
- Unusual odors (sweaty feet, isovaleric acidemia; maple syrup, maple syrup urine disease)
- Hypoglycemia
- Jaundice
- Cardiomyopathy (Pompe disease, mitochondrial respiratory chain defect)

Diagnosis

If an IEM is suspected, obtain screening studies *and* if possible save additional blood and urine prior to the initiation of therapy. Initial studies are listed in ▶ Box 47.2.

Although serum lactate is an essential study during the workup of an infant with a suspected IEM, elevations should be interpreted with caution. High plasma lactate can be due to tissue hypoxia secondary to shock, excessive endogenous or exogenous catecholamines, or poor hepatic clearance.

Simultaneous arterial lactate and pyruvate levels are essential in the infant with a metabolic acidosis thought secondary to an IEM. The lactate/pyruvate ratio (normal 10–20:1) can aid in the diagnosis of disorders of pyruvate and carbohydrate metabolism as well as certain respiratory chain defects. The lactate to pyruvate ratio is typically elevated in respiratory chain defects and pyruvate carboxylase deficiency and normal (both lactate and pyruvate elevated) in pyruvate dehydrogenase deficiency, glycogen storage disease type 1, and fructose 1,6-DP deficiency. Lactate elevations should be interpreted with caution. High plasma lactate can be due to tissue hypoxia secondary to shock, excessive endogenous or exogenous catecholamines, or poor hepatic clearance. Key laboratory findings are summarized in ◘ Table 47.5.

The combination of certain findings can suggest a specific IEM:

- Low glucose + low to no urine ketones + mild to moderate increased NH_3 → Consider fatty acid oxidation defect.
- Low glucose + urine ketones +/– hepatomegaly → Consider galactosemia, glycogen storage disease, or disorders of gluconeogenesis.
- Anion gap metabolic acidosis + normal lactate + mild to moderate increased NH_3 → Consider organic acidemias.
- Anion gap metabolic acidosis + elevated lactate and normal pyruvate → Consider respiratory chain defects.

- Anion gap metabolic acidosis + elevated lactate and pyruvate → Consider pyruvate dehydrogenase deficiency and pyruvate carboxylase deficiency.
- Anion gap metabolic acidosis + elevated lactate and pyruvate + low glucose → Consider glycogen storage disease type 1 and fructose 1,6-DP deficiency.
- High NH_3 + normal glucose + respiratory alkalosis → Consider urea cycle defect.

Box 47.2 Initial Laboratory Studies in the Evaluation of an IEM

- Glucose
- Electrolytes with anion gap
- Urine ketones and reducing substances
- Blood gas
- Ammonia (NH_3)
- Lactate
- Pyruvate
- Liver function tests, total and direct bilirubin
- Renal function tests
- Complete blood cell count
- Serum and urine amino acids
- Urine organic acids
- Total and free carnitine
- Acyl carnitine profile

High clinical suspicion + key laboratory abnormalities = Diagnosis of IEM

47.5.4.4 Management

Treatment of a suspected IEM must commence prior to a definitive diagnosis with the correction of metabolic derangements (e.g., hypoglycemia, acidosis, and electrolyte abnormalities), the prevention of further catabolism, and the removal of accumulating metabolites.

The treatment of a suspected IEM must commence prior to a definitive diagnosis. The initial management consists of the correction of metabolic derangements such as hypoglycemia, acidosis and electrolyte abnormalities, the prevention of further catabolism, and the removal of accumulating metabolites. The prevention of catabolism is best accomplished by providing adequate glucose and limiting protein intake.

The most notable accumulating metabolites are ammonia with urea cycle defects and organic acid intermediates with organic acidopathies. Ammonia scavengers such as sodium benzoate (250 mg/kg/day) and sodium phenylacetate (250 mg/kg/day) should be administered if marked elevations in ammonia exist. Arginine (250–700 mg/kg/day) is an essential intermediary amino acid in certain urea cycle defects and should be administered pending definitive diagnosis in infants with hyperammonemia.

The accumulation of organic acid intermediates may require sodium bicarbonate therapy for severe acidosis. Methylmalonic acidemia and multiple carboxylase deficiency may be responsive to vitamin B_{12} and biotin, respectively. The administration of carnitine (50–100 mg/kg/day) should also be considered as carnitine is excreted bound to organic acids. Severe hyperammonemia, due to urea cycle defects or refractory acidosis due to organic acidemia, often requires the early institution of hemodialysis for toxin removal.

Table 47.5 Key laboratory findings in inborn errors of metabolism

Laboratory finding	Urea cycle defect	Organic acidemia	Glycogen storage disease	Disorders of fatty acid oxidation	Mitochondrial respiratory chain defect	Galactosemia
Glucose	Normal	Low to normal	*Low*	*Low*	Low to normal	*Low*
Acid–base	*Respiratory alkalosis*	*Anion gap acidosis*	*Anion gap acidosis*	Normal to acidosis	*Anion gap acidosis*	Normal to acidosis
Ammonia	*High*	Normal to elevated	Normal	Normal to moderately elevated	Normal to moderately Elevated	Normal
Urine	Normal to Elevated	*Elevated ketones*	*Elevated ketones*	*Low ketones*	*Normal*	*Positive reducing substances*
Lactate[a]	Normal	Normal to elevated	*Elevated*	Normal	*Elevated*	Normal
Pyruvate	Normal	Normal	*Elevated*	Normal	Normal	Normal
Other	*Cerebral edema*	*Unusual urine odor*	*Enlarged liver, cardiomyopathy*	*Presentation during intercurrent illness, cardiomyopathy*	*High L/P ratio, systemic cytopathology*	*Liver dysfunction, renal tubular acidosis, cataracts*

[a] Although serum lactate is an essential study during the workup of an infant with a suspected IEM, elevations should interpreted with caution. High plasma lactate can be due to tissue hypoxia secondary to shock, excessive endogenous or exogenous catecholamines, and poor hepatic clearance.

Review Questions

1. Which statement best describes important physiologic differences in the respiratory system between the small infant and the older child or adult?
   - A. A much larger portion of total airway resistance occurs in the upper airway of an infant than in an adult.
   - B. The chest wall of an infant is highly non-compliant with significant outward elastic recoil to balance the inherent tendency of the lung to collapse.
   - C. The larynx of the infant is more cephalad and anterior than that of an adult or older child.
   - D. The small infant has twice the density of type 1 muscle fibers which allows them to be at less risk for early respiratory fatigue.
   - E. The upper airway of the infant is more pliable and, therefore, more resistant to obstructive forces.

2. Which statement best describes important physiologic differences in the cardiovascular system between the small infant and the older child?
   - A. Autonomic innervation of the infantile myocardium is functionally immature because of a low density of β-adrenergic receptors.
   - B. The individual neonatal cardiac myocytes are composed of equal amounts of contractile elements (actin, myosin, troponin, and tropomyosin) as a mature heart and, therefore, are dependent on chronotropy to assure adequate cardiac output.
   - C. The infant heart, highly dependent on chronotropy, is vulnerable to bradycardia due to a state of early parasympathetic dominance.
   - D. The infantile myocardium is characterized by a high ventricular compliance.
   - E. The neonatal cardiac myocytes have a relatively mature sarcoplasmic reticulum making them less reliant on extracellular calcium.

3. Which of the following statements concerning the immature central nervous system of the infant is MOST accurate?
   A. Axodendritic growth ceases shortly after birth (within the first month of life).
   B. Open fontanels confer complete protection against acute increases in intracranial pressure.
   C. The dura mater is highly compliant in the infant, providing protection against acute increases in intracranial pressures.
   D. The myelination of axons continues up to 6 years of age.
   E. The number of glial cells (astrocytes, oligodendrocytes) attains adult levels at birth or shortly thereafter (within the first month of life).

4. Which of the following statements most accurately describes the mechanisms that contribute to the ability of the infant to maintain a normal temperature?
   A. Although the infant may have difficulty maintaining normothermia, the lack of normothermia is of little consequence.
   B. Infants are at increased risk for heat loss and have immature mechanisms to respond to heat loss.
   C. Infants are at increased risk for heat loss but have relatively mature mechanisms to respond to heat loss.
   D. Infants are not at increased risk for heat loss and have relatively mature mechanisms to respond to heat loss.
   E. Infants are not at increased risk for heat loss but have immature mechanisms to respond to heat loss when it occurs.

5. A 2-week-old infant presents with lethargy and clinical signs of shock, tachycardia, thready pulses, and delayed capillary refill. Point of care testing reveals a venous pH 7.32, CO_2 34 mm Hg, base deficit (−8), sodium 132 mMol/L, and glucose value of 28 mg/dL. In addition to ensuring an adequate airway and breathing, and administering a 20 mL/kg normal saline fluid bolus, the next most appropriate step in the stabilization of this infant includes which of the following?
   A. The administration of an intravenous $D_{25}W$ (25% dextrose solution) bolus at a dose of 2 mL/kg.
   B. The administration of antibiotics after blood is cultured and lumbar puncture is performed.
   C. The administration of hydrocortisone at a dose of 50 mg/m^2.
   D. The administration of sodium bicarbonate at a dose of 1 mEq/kg.
   E. The initiation of an intravenous infusion of prostaglandin E_1 at a dose of 0.05 mcg/kg/min.

6. Which of the following statements regarding neonatal infections is true?
   A. Acyclovir is ineffective at reducing morbidity in herpes simplex virus disease of the neonate.
   B. All critically ill infants should be treated empirically with broad-spectrum antibiotics until a definitive diagnosis is established.
   C. Enterococci account for the majority of cases of neonatal sepsis.
   D. Late-onset group B streptococcal infection often presents as circulatory collapse and is a more fulminant disease than early-onset infection.
   E. The lack of cutaneous lesions rules out disseminated herpes simplex virus disease in the neonate.

7. Which of the following statements is true regarding infantile botulism?
   A. Constipation is often the initial symptom of infantile botulism.
   B. Infantile botulism is characterized by ascending paralysis initially involving the lower extremities and sparing the cranial nerves.

C. Infantile botulism is characterized by neuromuscular dysfunction due to a neurotoxin that binds irreversibly to the postsynaptic acetylcholine receptor.
D. The ingestion of formed botulinum toxin from contaminated foods or soil is the cause of infantile botulism.
E. Tobramycin is the preferred antibiotic for treatment of infantile botulism.

8. A 4-month-old infant presents with profound diarrhea, cyanosis, and tachypnea. Clinical exam reveals a regular heart rate and rhythm with no evidence of a gallop or murmur. Breath sounds are clear in all lung fields. Chest radiograph reveals clear lung fields with a normal cardiothymic silhouette. Despite placing the infant on supplemental oxygen, pulse oximetry on the left foot reveals an oxygen saturation value of 85%. Blood aspirated from the right radial artery appears dark and blood gas analysis reveals a pH 7.30, $PaCO_2$ 33 mm Hg, PaO_2 99 mm Hg, and a base deficit of (−11). Which of the following is the most likely explanation for this clinical scenario?
A. An air bubble in the blood gas sample
B. Carboxyhemoglobinemia
C. Methemoglobinemia
D. Right to left shunting at the atrial level
E. Right to left shunting through a patent ductus arteriosus

9. An infant presents with profound lethargy and symptoms of an upper respiratory tract infection. He is afebrile. Point of care blood testing reveals a mild metabolic acidosis and a glucose level of 34 mg/dL. Urine dipstick testing is negative for both reducing substances and ketones. There is no unusual odor to the urine. As you begin a comprehensive workup and treatment plan, you share with the team your suspicion that the infant most likely has which of the following IEM?
A. Fatty acid oxidation disorder
B. Galactosemia
C. Glycogen storage disease
D. Organic acidemia
E. Urea cycle defect

10. A 1-week-old presents with lethargy and seizures. Initial laboratory workup is notable for an ammonia level of 1405 μMol/L and a mild respiratory alkalosis. The serum lactate and glucose levels are normal. The most likely diagnosis for this infant is which of the following inborn errors of metabolism?
A. Fatty acid oxidation disorder
B. Galactosemia
C. Glycogen storage disease
D. Mitochondrial respiratory chain defect
E. Urea cycle defect

11. A 4-month-old infant undergoes magnetic resonance imaging to evaluate a congenital intracranial cyst. He has had no past history of breathing difficulty. The procedure is performed under deep sedation without endotracheal intubation. At the completion of the procedure, the infant is noted to be tachypneic with a respiratory rate of 54 breaths/min. Pulse oximetry indicates an oxygen saturation of 88%. There are decreased breath sounds over the right lung field. The chest radiograph reveals opacification of the right thorax with volume shift to the right. Which of the following explanations for this clinical scenario is MOST likely?

A. The infant has a right-sided chest anomaly commonly found in association with congenital intracranial cysts.
B. The infant has aspirated with gastric or salivary contents preferentially entering the right mainstem bronchus.
C. The infant has developed atelectasis because the mechanisms that maintain the functional residual capacity above the closing capacity have been compromised.
D. The infant has developed "flash pulmonary edema" from obstructed upper airway flow secondary to collapse of the highly compliant upper airway tissues secondary to sedation.
E. The infant has tracheobronchomalacia that has been exacerbated by the administration of sedation.

12. You are called to the ER to evaluate a 14-week-old infant with an 8-h history of tachypnea and cyanosis. The infant is being bottle-fed and lives on a farm with four older siblings. You observe the infant to have moderate intercostal retractions and tachypnea. Heart and lung sounds on examination are unremarkable. You place the infant on 100% oxygen and see that the child remains cyanotic with an oxygen saturation of 70%. You obtain a CXR and radiology confirms it is unremarkable. The abnormality associated with this infant's disorder is:
    A. Hemoglobin isomerase deficiency
    B. Neonatal polycythemia
    C. Methemoglobin reductase deficiency
    D. Methylene blue metabolism deficiency
    E. Glutathione reductase deficiency

13. A 2-day-old infant with hypoplastic left heart syndrome who is surgically unrepaired and remains on PGE_1 since birth is having saturations of 85–90%. To maintain Qp/Qs ratio balance closer to 1:1, all the following statements are incorrect EXCEPT:
    A. Use supplemental oxygen.
    B. Tolerate hypercarbia (PaCO2 45–50 mm Hg).
    C. Maintain a lower hematocrit (25–30%).
    D. Start an epinephrine infusion.
    E. Decrease dose of PGE_1.

14. A 3-week-old infant is admitted with signs and symptoms concerning for herpes encephalitis. A positive polymerase chain reaction (PCR) confirmation for herpes simplex virus (HSV) diagnosis from cerebrospinal fluid indicates:
    A. Herpes virus RNA is present in the CSF.
    B. Herpes virus DNA is present in the CSF.
    C. Herpes virus surface antigens are present in CSF.
    D. Herpes virus proteins are present in the CSF.
    E. Herpes virus immunoglobulins are present in the CSF.

Answers

1. C
2. C
3. D
4. B
5. A
6. B
7. A

8. C
9. A
10. E
11. C
12. C
13. B
14. B

Suggested Reading

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Child Abuse

Caroline L. S. George

Contents

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Learning Objectives

1. Recognize patterns of injuries that support the likelihood that abuse was the etiology of the injuries.
2. Create a medical plan that utilizes radiologic studies, laboratory tests, and retinal examination to evaluate a child for abusive head trauma, abusive abdominal trauma, and fractures.
3. Distinguish roles of critical care physicians, child abuse pediatricians, and other professionals and understand how they complement each other in the medical evaluation of child abuse and neglect.
4. Understand the spectrum of presentation that occurs with caregiver-fabricated illness and medical maltreatment.
5. Recognize how biases and barriers can prevent a medical team from placing child abuse and maltreatment in a differential diagnosis.

48.1 Epidemiology

The Department of Health and Human Services receives data on the number and types of reports of child maltreatment made through local agencies to the National Child Abuse and Neglect Data System. In 2016 there were just over 675,000 cases of child abuse and neglect reported to child protection services in the United States of America. Approximately 1750 children died due to abuse and/or neglect in that same year. In 2016, approximately 75% of all cases reported to child protection services were cases of neglect, 18% were due to physical abuse, 9% were due to sexual abuse, and the remaining were due to "other" types of abuse. Almost 15% of children were victims of more than one type of abuse, such as neglect and physical abuse. Very young children (<4 years of age) made up almost 35% of victims of child maltreatment, and the most vulnerable children (<12 months of age) made up almost 15% of all child abuse victims. This point is important for all pediatricians to understand that those children who cannot communicate well are the children at highest risk for being a victim of abuse and thus our roles as diagnosticians and mandatory reporters are important for their care.

48.2 Barriers and Biases

The use of evidence-based guidelines may prevent implicit bias from impacting which child receives a child abuse evaluation.

There are many barriers to placing "child abuse" in a patient's differential diagnosis. We, as medical providers, unknowingly bring various types of biases with us during the assessment of a patient. For example, *preconceived bias* about a family's socioeconomic status can influence when child abuse and neglect is diagnosed. Research has shown that poverty, by itself, does not cause child abuse and neglect; rather, there is an association. Despite this lack of causality, a retrospective study demonstrated that children on public insurance were more likely than children on private insurance to have a skeletal survey performed to look for occult abusive injuries. *Fixation errors* may cause the medical team to focus on one piece of information while ignoring other pertinent data. An example of this error is focusing on the medical needs of diagnosing and treating a fractured femur while ignoring a patterned bruise to the face, thus failing to place physical abuse in the differential diagnosis. Finally, *knowledge errors,* due to a lack of training or familiarity with the rapidly growing medical literature in the specialty of child abuse pediatrics, can prevent abuse and neglect from being placed in a differential diagnosis when appropriate. Utilizing evidence-based guidelines and protocols assist medical teams in caring for these critically ill children by limiting implicit bias. The

additional benefit of applying standardized protocols may remove the stress and burden felt by the medical team when an abuse evaluation is undertaken. For example, presenting a skeletal survey or retinal examination as a standard of care when communicating with the patient's caregivers is likely to be less stressful for all.

48.2.1 Presentation of the Critically Ill Abused Child

Delayed presentation and medical therapies occur in pediatric victims of abusive trauma. This can have a negative impact on the clinical outcome of this patient population.

It has been hypothesized that the presentation of victims of child physical abuse to medical care is different from accidental trauma victims and this subsequently influences how the medical teams approach these patients. Research is starting to address this hypothesis. In one study, pediatric trauma victims in the United Kingdom were assessed for adherence to "best practice standards." Children with suspected physical abuse injuries were less likely to be referred to a trauma center and had worse outcomes compared to accidental injury patients. The reason for this is that patients were more likely to benefit from a trauma center and protocol-directed care when the patient was "announced" as a trauma victim. This is a simple but important point for critical care physicians as the extent of injuries may be underrecognized and institution of therapies may be underutilized and delayed because a victim of child physical abuse may not present as a known or obvious trauma victim. These delays can have a negative impact on patient outcomes. ◘ Figure 48.1 provides a visual reminder of the severity of abusive trauma and the underdiagnosed and underresuscitated state in which these children may present to medical care.

48.3 Cutaneous Injuries

Immobile children who present with a bruise need to have the bruise addressed within the history of presenting illness, in association with a medical and physical abuse evaluation.

The medical record should reflect the size, location, type of skin finding, and either photo documentation or body surface diagram documentation of any cutaneous findings when child physical abuse is in the differential diagnosis.

Bruises are the most common cutaneous sign of physical abuse, yet they frequently occur from normal childhood activities and accidental injuries too. As expected, developmentally mobile children are more likely to have a bruise because of their motor skills. The quote "those who don't cruise rarely bruise" comes from a study designed to determine the frequency and location of bruises in infants and toddlers. Unless a child was cruising or walking, it was very rare (<2%) for children to have a bruise, while ~50% of children with the ability to walk had a bruise. The conclusion is that immobile infants should not have bruising and a prompt evaluation for medical conditions and physical abuse should proceed if bruising is observed. Common bruises that occur during normal childhood activities are those that occur over bony prominences such as the forehead, knees, and shins. The importance of these locations is that they are common points of impact during falls, impact injuries, and sports injuries. Furthermore, most accidental events associated with bruising cause a single bruise, while it is much less common (<5% of the time) for accidental events to be associated with ≥3 bruises. A key study in a critical care unit in 2010 provided the groundwork to help distinguish bruises caused by inflicted trauma from those caused by accidental trauma. This retrospective study, and others that have followed, resulted in a clinical decision tool based on age that helps clinicians identify bruises that bring physical abuse into a patient's differential diagnosis. In the original study, when this body region age-based clinical tool was applied to the study group, it correctly predicted children with inflicted bruises with 97% sensitivity and 84% specificity. Currently, this clinical tool has evolved into the mnemonic "TEN-4 FACES-p" (◘ Table 48.1). When this tool is used, the torso specifically refers to the area from the shoulders (and biceps) to the upper thighs. The number "4" refers to any bruise on a

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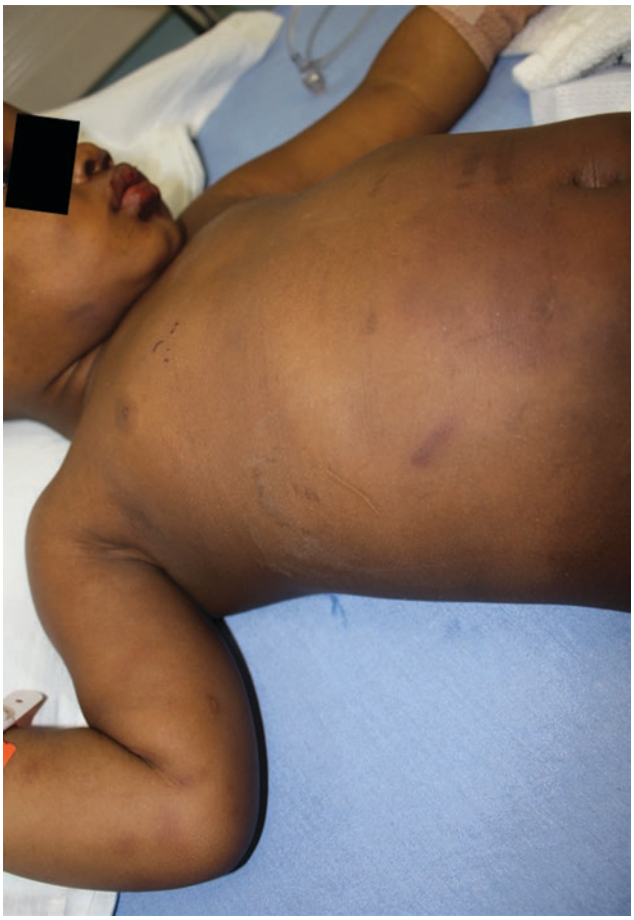

Fig. 48.1 A 25-month-old male presented to a pediatric trauma center with a history of falling from a toy bicycle 2 days prior. This photo documentation obtained in the emergency department demonstrates a distended abdomen and a small portion of the cutaneous injuries observed. At this moment in time, there were two known intraparenchymal brain bleeds and a small amount of intracranial extra-axial hemorrhage, and suspicion of blunt abdominal trauma from a FAST. This figure demonstrates a lack of cardiopulmonary monitoring, and IV fluid administration had just started >2 hours after presentation. Very likely, more intensive medical monitoring and therapies would have been instituted if the patient had presented as an accidental trauma victim with the same diagnoses. (Photo documentation provided by Caroline George, MD)

Table 48.1 TEN-4 FACES-p clinical decision rule

TEN-4	FACES-p
Torso Chest Abdomen Back Buttocks Genitourinary	**F**renulum
	Angle of the jaw
	Check (buccal surface)
	Eyelid
Ear	**S**ubconjunctival hemorrhage
Neck	"**p**" = any patterned bruise
4 = Any bruise on a child <4.99 months of age *or* bruises in the TEN FACES region on a child ≤4 years of age	

Pierce, MC. Accidental Versus Non-Accidental Bruising: An Evidence-Based Approach. InterCAP: International Course on Child Abuse Paediatrics. Amsterdam, 2017. Reproduced with permission from Dr. Mary Clyde Pierce

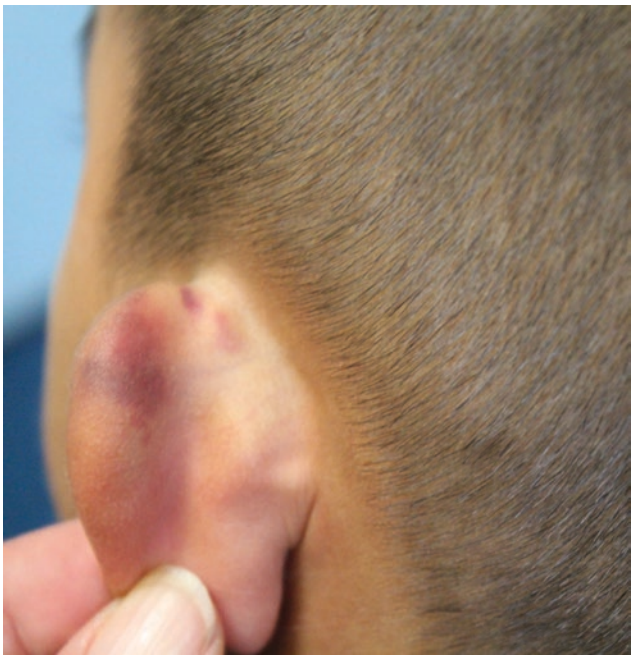

Fig. 48.2 A 13-month-old male physical abuse victim with left ear bruising. Bruising was present on both the anterior and posterior parts of the pinna. (Photo documentation provided by Sonja Eddleman, MSN, RN, CA/CP SANE, SANE-A, SANE-P)

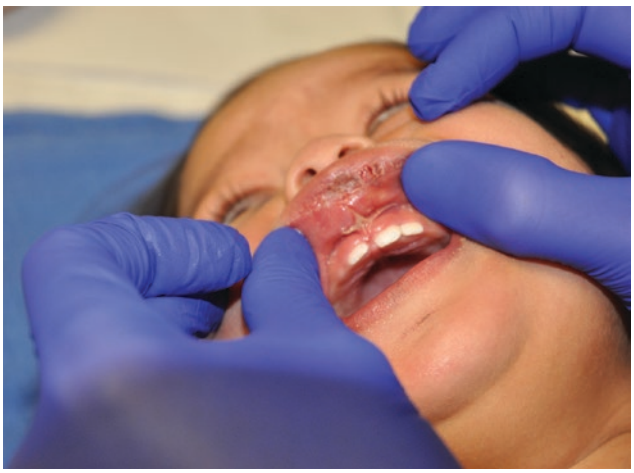

Fig. 48.3 A 10-month-old female physical abuse victim with upper lip bruising and an upper labial frenulum injury. (Photo documentation provided by Sonja Eddleman, MSN, RN, CA/CP SANE, SANE-A, SANE-P)

child <4.99 months of age and bruises in the TEN FACES region on a child ≤4 years of age (Figs. 48.2, 48.3, and 48.4). Patterned bruises are cutaneous injuries left by an object used as a weapon. Some patterned skin findings may assist medical providers in identifying what type of weapon was used to harm the child. Findings such as a hand slap, a loop mark from a flexible cord, or a bite mark have characteristic shapes that are important to diagnose as inflicted trauma (Figs. 48.4 and 48.5). Finally, how these cutaneous markings are documented in the medical record is important for communication to other providers and law enforcement or child protection services. Photo documentation with a measurement tool obtained by one skilled in photo documentation is the optimal method. When photo documentation is not available, measuring the injuries and documenting the location, shape, and color on a body surface diagram in an electronic medical record can also convey important information (Fig. 48.6). With this method, diagnosing the skin injury as a bruise, hematoma, or abrasion, for example, within the physical examination portion of the medical note is a required element to complete the skin assessment.

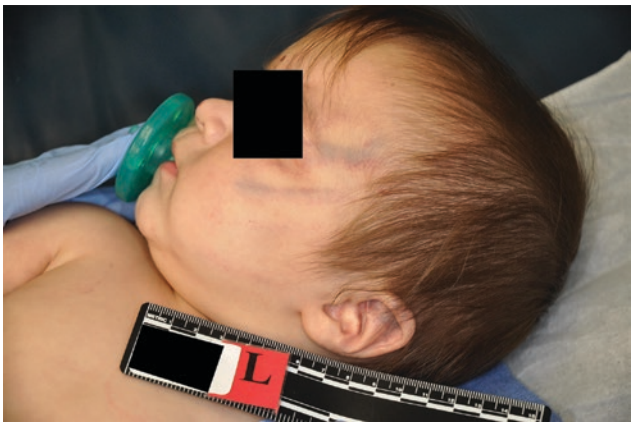

Fig. 48.4 A 13-month-old female physical abuse victim with linear patterned bruise to the left face consistent with a slap mark. The two more superior linear markings are wider than the two more inferior markings. Also note bruising to the left ear. (Photo documentation provided by Sonja Eddleman, MSN, RN, CA/CP SANE, SANE-A, SANE-P)

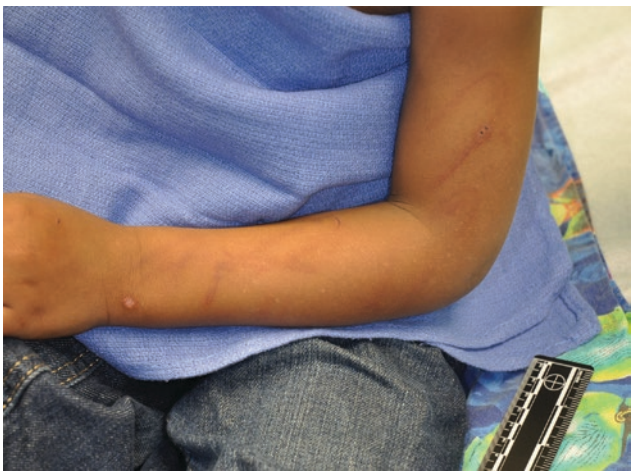

Fig. 48.5 A 4-year-old male physical abuse victim with multiple loop marks to the upper left extremity created by being whipped with a flexible cord. (Photo documentation provided by Sonja Eddleman, MSN, RN, CA/CP SANE, SANE-A, SANE-P)

Abusive head trauma is the preferred term that encompasses all types of inflicted trauma to the head.

48.4 Abusive Head Trauma

48.4.1 Definitions

Traumatic brain injury (TBI) is a common cause for admission to the PICU, and abusive head trauma is the most common fatal type of physical abuse in children. According to the Centers for Disease Control and Prevention (CDC), TBI is common in children ranging from 1100 to 2200 cases/100,000 children 0–4 years of age (US population) during the years 2001–2010. Nonfatal abusive head trauma is most common in those less than 12 months of age with a peak incidence at 1–3 months of age. First, it is important to acknowledge the different terms used to describe head injury due to abuse. Historically, the term "shaken baby syndrome" characterized the constellation of symptoms described by Dr. Caffey, consisting of subdural hemorrhage (SDH) and long bone fractures. Due to radiologic, biomechanical, histopathology, and clinical studies on the pathophysiology of inflicted head trauma, the term "shaken baby syndrome" fails to represent the variety and combinations of mechanisms causing this type of trauma. Further, the term "shaken baby syndrome" presumes the medical providers making this diagnosis have knowledge that a

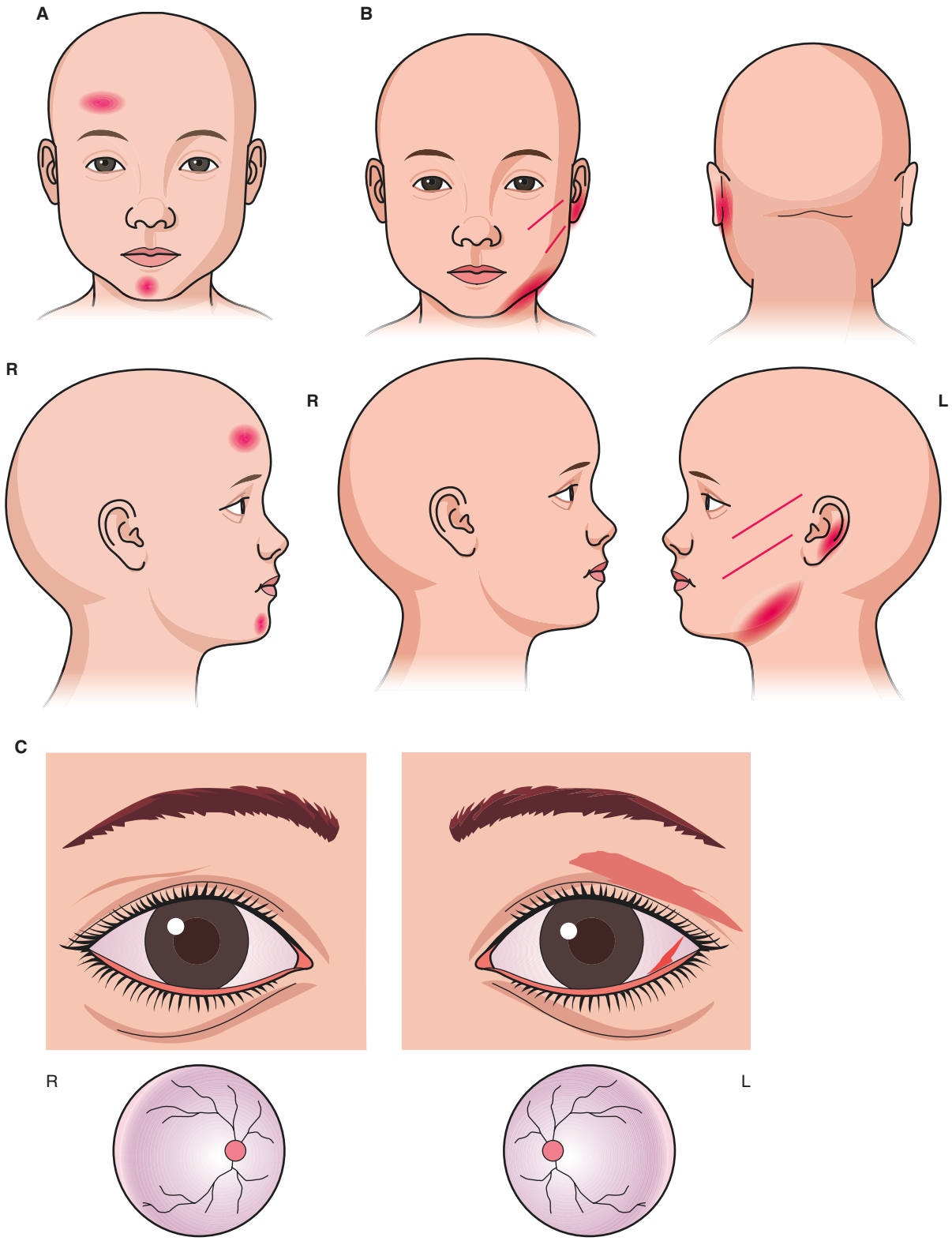

Fig. 48.6 Pictorial documentation of cutaneous findings in an electronic medical record (EMR): Panel A. Demonstrates the location of skin findings over the bony prominence of the right forehead and the chin, locations common in ambulatory children. Panel B. Demonstrates cutaneous injury to the left ear and along the left angle of the jaw. Patterned linear markings across the left buccal surface of the check are also demonstrated. These locations and characteristics are typical for abusive injury. Panel C. Demonstrates locations of and color of injury resulting in a left subconjunctival hemorrhage and left upper eyelid bruising. These are injuries that would not commonly occur due to an accidental injury in a non-mobile child. In all examples, the physical examination would need to describe the type of injury as a bruise, hematoma, etc. (Drawing tool application from Epic EMR, © 2019 Epic Systems Corporation. Used with permission)

shaking injury mechanism caused the injury, when in fact many times an accurate history is not provided to the medical team. The American Academy of Pediatrics in 2009 recommended the use of the term *abusive head trauma* (AHT) to include all mechanisms of inflicted injury such as blunt impact, spinal cord injury, and secondary hypoxic brain injury, in addition to a shaking mechanism. Frequently, however, everyday language still refers to all types of AHT as "shaken baby syndrome," causing confusion. For this reason, it is important for the medical record to use accurate and current terminology.

48.4.2 Mechanisms and Forces

Contact mechanisms cause injury due to direct focal forces and translational inertia on the scalp, skull, brain, and surrounding tissues. Vigorous shaking causes rotational inertial forces on the brain and surrounding structures.

There are two broad categories of AHT based on two general mechanisms of injury. Direct-contact mechanisms of injury produce forces by direct impact with or without translational inertial forces resulting in *focal injuries*. Repetitive acceleration-deceleration mechanisms of injury produce rotational inertial forces resulting in *diffuse injuries*. Each category of force is associated with specific injury characteristics reflected in clinical findings and radiographic diagnoses (► Box 48.1). The resulting diagnoses associated with a focal impact injury are due to direct contact over a relatively small surface area of the patient's head with an object and resulting translational inertia. The resulting diagnoses associated with acceleration-deceleration injury, as seen with violent shaking, reflect diffuse rotational inertial forces over the large surface area of the brain, the cervical spinal column, and surrounding tissues. As described in ► Box 48.1, some findings such as SDH can result from either a contact or diffuse (i.e., noncontact) mechanism of injury, while other findings such as scalp hematoma or skull fracture occur only following a contact injury. Thus, a physical examination and radiological studies complement each other in defining the type of mechanism(s) that were required to cause the injury(s). As with all types of TBI, children that are victims of AHT are also at risk for *secondary* brain injuries. Common clinical findings associated with secondary injuries include hypoxemia due to apnea and seizures. Because the abusive injuries may be associated with a delay in seeking medical care, preventing further secondary injury is paramount to the patient's outcome. In summary, defining the types of mechanisms that cause the observed injuries, by characterizing their description and location, conveys important information regarding the patient's diagnosis and prognosis.

Box 48.1 Classification of Traumatic Brain Injuries

Primary injuries

Focal injuries

1. Contact injuries
   - Soft tissue injuries
   - Skull fractures or deformations
   - Epidural hematomas
   - Subdural hematoma
   - Superficial cortical contusions
   - Lacerations
2. Translational inertial
   - Cortical contusions (contrecoup)
   - Lacerations
   - Intracerebral hematomas
   - Subdural hematomas

- Subarachnoid hemorrhages
- Petechial hemorrhages

Diffuse injuries

1. Acceleration-deceleration-rotational inertia
   - Concussions
   - Subdural hematomas
   - Subarachnoid hemorrhages
   - Petechial hemorrhages
   - Contusional tears
   - Traumatic axonal injuries

Secondary injuries

1. Hypoxic-ischemic injuries
   - Cerebral edemas (vasogenic, cytogenic)
   - Infarction
   - Metabolic derangements
2. Pressure injuries
   - Infarction
   - Herniation syndromes

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48.4.3 Radiologic Imaging

Head CT, and brain and spine MRI studies complement each other in diagnosing the type and extent of abusive head trauma.

Diagnosing any type of TBI relies heavily on radiologic studies. In the practice of child abuse pediatrics, the type of study and timing also play critical roles in diagnosing the specific forces that caused the injuries. Head computed tomography (CT) without IV contrast is a part of any initial TBI evaluation. Shortly after presentation to medical care, a head CT allows a quick detection of scalp edema and hematomas, skull fractures, SDH, subarachnoid hemorrhage (SAH), and signs consistent with ischemic brain injury (loss of gray-white matter differentiation). The first steps in diagnosing injury consistent with focal contact, diffuse forces, or combination of these can be identified by head CT (◘ Figs. 48.7, 48.8, and 48.9). Head magnetic resonance imaging (MRI) without contrast utilizing the T1- and T2-weighted sequences plus gradient-echo sequences allows a better definition of thin-layer blood and CSF collections than a head CT. When brain and spine MRI studies are obtained within 24–48 hours of injury, additional information regarding brain edema and ischemia, spine ligamentous injury, and spinal cord hemorrhage and edema can be determined. Head MRI improves sensitivity and specificity for distinguishing the types of fluid collections including detection of neomembranes as might be found with chronic subdural hematomas with re-bleeding. Diffusion-weighted imaging (DWI) can aid specifically in the identification of areas where water has shifted from the extracellular to the intracellular compartment consistent with brain parenchymal ischemia and infarction. This short MRI sequence can detect parenchymal injury within minutes of the trauma occurring and can assist in identifying hypoxic-ischemic damage in AHT. Evaluation of DWI sequences of infants and children with abusive versus accidental injury demonstrates those with abusive injury tend to have higher incidence of hypoxic-ischemic injury. It is unclear if this difference is due to different primary mechanisms of injury or more severe secondary mechanisms of brain injury in abused children. The current standard of care recommends brain and spine MRI studies

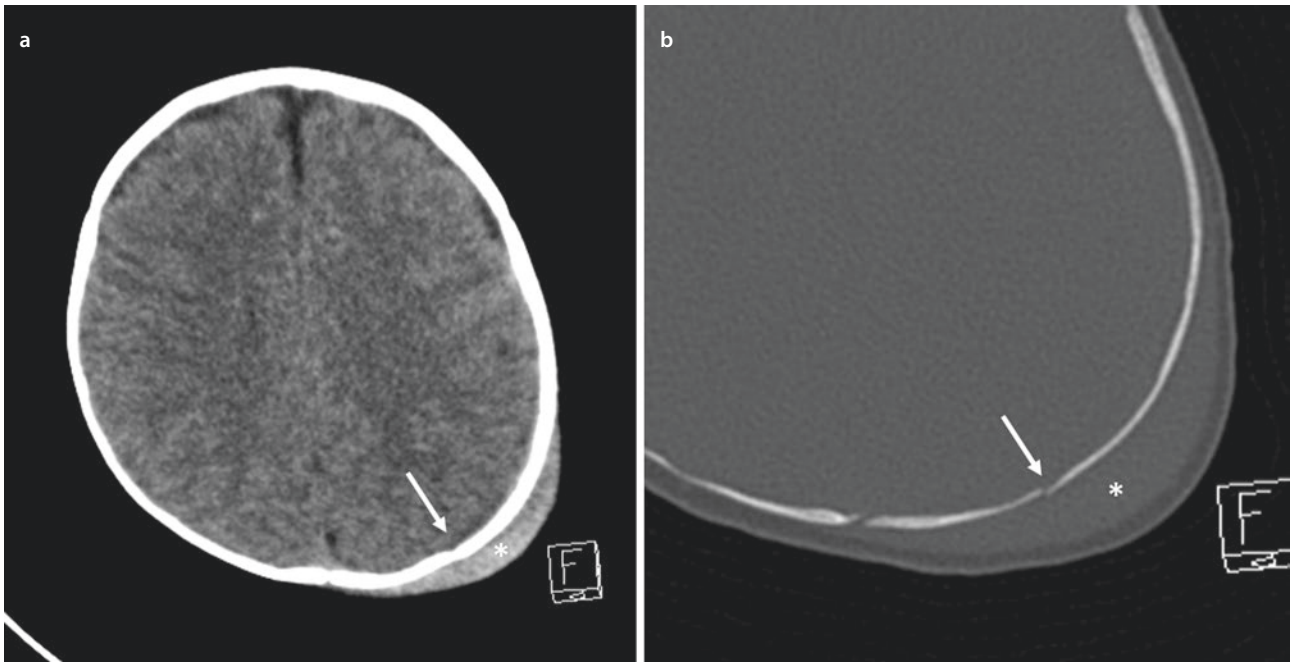

Fig. 48.7 A 4-month-old infant suffered cranial injuries from a short fall. This contact force resulted in scalp edema (asterisk) located left and posterior. This finding was present on physical examination and by axial head CT brain window **a** and bone window **b** images. An underlying linear skull fracture (white arrows) is diagnosed by head CT. (Head CT images provided by Caroline George, MD)

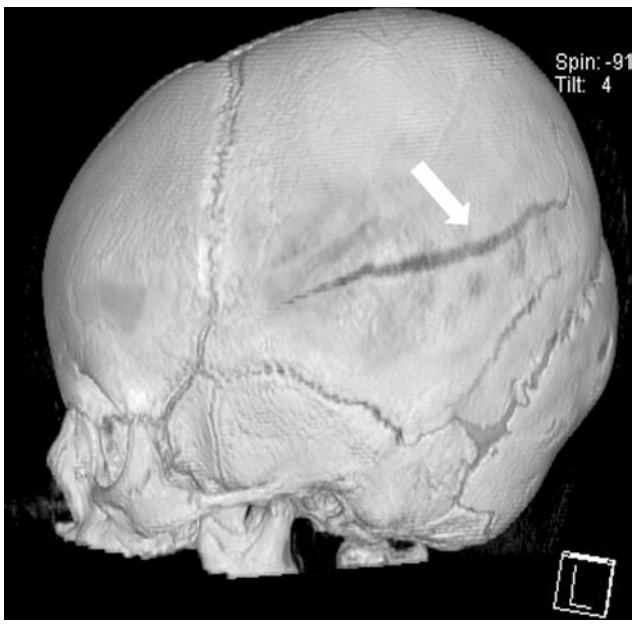

Fig. 48.8 3-D reconstructed surface-rendered images of the skull bones from the patient presented in Fig. 48.7. A left linear parietal skull fracture is demonstrated (arrow). (Head CT image provided by Caroline George, MD)

with DWI sequences be obtained within the first 24–48 hours after presentation so that diagnoses of diffuse force brain and spinal cord injury and secondary brain injury can be made. The future of screening for TBI using non-radiologic methods will likely utilize biomarkers that can detect brain injury shortly following an injury. The sensitivity and specificity of this type of

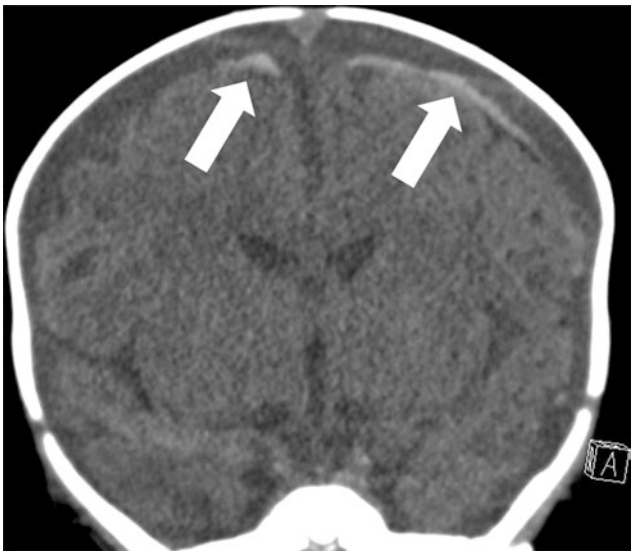

Fig. 48.9 Coronal head CT image of a 4-month-old infant with prominent extra-axial spaces and subdural hemorrhage (arrows). This infant also had severe retinal hemorrhages and lacked clinical or radiographic signs of a blunt force contact injury. These findings collectively aided the diagnosis of diffuse repetitive rotational forces caused by abusive head trauma. (Head CT image provided by Caroline George, MD)

testing are not advanced enough at this point. Therefore, protocols based on clinical findings, developmental ability, and age of the child direct the utilization of radiologic studies in child abuse evaluations.

48.4.4 Subdural and Subarachnoid Hemorrhages

A subdural space is not present in a normal healthy dura mater. The dural border cell layer contains less structural support making this area susceptible to injury.

Knowing the anatomy of subdural and subarachnoid hemorrhages assists in understanding the mechanical forces and mechanisms of injury in AHT. The dura is not simply a fibrous membrane; rather, it contains three cell layers. The two outer dural cell layers contain collagen. The third cell layer, which abuts the arachnoid, is called the dural border cell layer. This cell layer is composed of flattened fibroblasts that lack both tight junctions and extracellular collagen. These structural differences make this cell layer within the dural membrane susceptible to shear injury. Cerebral veins, intradural vascular plexus, and arachnoid granulations carry blood and CSF to the superior sagittal sinus through complex intradural channels and vascular connections. Disruption of the relatively weak dural border cell layer results in dissection of blood and possibly CSF into this potential space. Thus, hemorrhage described in the subdural space may be more accurately described as a subdural compartment hemorrhage since a true "intradural" space does not exist unless it is created. The subarachnoid space is an anatomic space that lies under the arachnoid membrane and contains fibrous trabeculations, CSF, and bridging veins. Traumatic brain injury can also result in hemorrhage within this natural space.

48.4.5 Spine Injuries

Due to normal developmental differences, the cervicomedullary junction in infants may be particularly susceptible to diffuse rotational forces.

Despite the well-described fact that infants are predisposed to occipitocervical and upper cervical spine injuries due to a large head and weak neck muscles relative to an older child, evaluating the spine in the setting of AHT has been a relatively new diagnostic focus. Further contributing to this lack of attention to the spine are traditional autopsy techniques that disrupt the cervicomedullary junction, a site that may preferentially be affected by a shaking acceleration-deceleration mechanism of injury and diffuse forces. Thus, changing

autopsy practice that preserves the continuity of brain and cervical spine has resulted in identifying spine injury in up to 70% of fatal cases of AHT. These autopsy findings are consistent with MRI findings of nonfatal cases of AHT. Interestingly, while cervical cord ligamentous injury and cord hemorrhage are more common than previously thought, cervical spine fractures are relatively rare, diagnosed in <5% of skeletal surveys performed for the evaluation of occult bone injury.

48.4.6 Retinal Hemorrhages

In the setting of abusive head trauma, vitreoretinal traction is believed to cause retinal hemorrhages due to the repetitive diffuse rotational forces on the infant's head and body.

The evaluation for retinal hemorrhages (RHs) in a child abuse evaluation should, at a minimum, accompany any evaluation of AHT with associated intracranial hemorrhage in a child <12 months of age. Other clinical scenarios may also benefit from an ophthalmology examination. Approximately 75% of young children with intracranial injury due to AHT will have RHs, and thus, the presence of severe RHs adds significantly to the likelihood that abuse is the etiology of the injuries. Important for the critical care physician is the knowledge that RHs occur in children due to accidental traumatic and nontraumatic pathologies. The most common etiology of RHs in young children is the birth process. Approximately 30% of healthy newborn babies will have RHs identified when evaluated within hours of birth. Numerous studies demonstrate these RHs are located primarily toward the posterior pole of the retina (zone I, the most central 5% of the retina), yet some newborns will have RHs that extend out to zone III of the eye (the outer 25% of the retina). The majority of these infants have a number of RHs that are countable during an ophthalmologic examination (i.e., <20 hemorrhages). Approximately 90% of the RHs observed at birth resolve by 2 weeks of age. Rarely, a discrete RH can persist to 6 weeks of age. Critical illness is also associated with RHs. Again, most of these patients have <20 RHs identified. Patients with >20 RHs due to critical illness have experienced severe accidental head trauma or systemic disease such as leukemia with or without coagulopathy. Cardiopulmonary arrest and chest compressions in children are very rarely associated with RHs. Typically, RHs associated with CPR occur in patients with other pathologies. Thus, while RHs may be relatively common in critically ill children, they are few in number (i.e., <20), and severe RHs are observed only in those with coagulopathy or severe systemic disease. What helps distinguish RHs in AHT from other causes are the location and severity. When RHs are identified in patients with brain injury following diffuse forces, they are frequently described as "too numerous to count," and approximately 66% of eyes are characterized as occurring in multiple layers of the retina. The repetitive rotational mechanism of AHT is also specifically associated with RHs that extend from the posterior pole (zone I) out to the retinal periphery (zone III). Therefore, RHs described as "too numerous to count," observed in multiple layers of the retina, and extend out to the ora serrata of all four quadrants of the eye are highly suggestive of abuse when found associated with intracranial injury in the absence of severe accidental trauma.

The pathophysiology of traumatic RHs in pediatric patients is hypothesized to be due to vitreoretinal traction during repetitive rotational forces. Because of the strong correlation of RHs with AHT and the fact that they start to resolve quickly, the ophthalmologic examination should be obtained preferably within 24 hours and no longer than 72 hours after presentation to medical care. In clinical scenarios where frequent neurologic examinations may be medically required, the importance of a dilated retinal examination needs to be carefully considered for diagnostic and prognostic reasons. This situation is

best served by a team approach including critical care, neurosurgery, ophthalmology, and a child abuse pediatrician to expeditiously evaluate the patient for signs that aid in making a diagnosis of accidental vs AHT.

48.4.7 Constellation of Findings in AHT

Apnea and retinal hemorrhages are the two most significant distinguishing factors that are predictive of abuse causing an intracranial injury in the absence of obvious trauma.

In child abuse pediatrics, rarely is a single finding pathognomonic for abuse; rather, it is the constellation of clinical and radiologic findings that support the diagnosis. Clinical research studies in child abuse pediatrics are difficult for obvious reasons. One powerful technique to address a specific clinical question in medicine is by performing a systematic review of the literature. In one systematic review performed to identify clinical features that could distinguish abusive from accidental head trauma in children, several findings were made. The probability of AHT could be estimated based on the combination of clinical findings when correlated with intracranial injury. In this type of child abuse study, the definitions of AHT and accidental TBI need to be clearly defined with strong evidence appropriately placing patients into the abuse and accidental trauma study groups. Once a collection of studies meeting these strict criteria were identified, a multilevel logistic regression analysis evaluated five discriminating factors: apnea, retinal hemorrhages, rib/skull/long bone fractures, seizures, and head or neck bruising. The results demonstrated apnea (PPV 93%, OR 17.06, $p < 0.001$) and retinal hemorrhages (PPV 71%, OR 3.504, $p = 0.03$) were the clinical symptoms and diagnoses most predictive of AHT. Furthermore, in children less than 3 years of age, when three or more discriminating factors were found in association with intracranial injury, the odds ratio was >100 (PPV 85%) that abuse was the etiology of the injury. In contrast, in the absence of any of the above-defined discriminating factors, intracranial injury in a young child in and of itself has an estimated probability for abuse as the etiology of 4%. Finally, some of the most compelling studies regarding the mechanism of injury are those that correlate confessions with the resulting brain injury. A study comparing confessions of repetitive rotational mechanisms of injury (i.e., violent shaking) to publicly witnessed accidental injuries confirmed the diagnostic value of SDHs and severe RHs and their relationship with diffuse brain injury. This prospective study purposefully evaluated for signs of impact to the head and found the *absence* of contact injury added diagnostic value to AHT.

48.5 Abdominal Injuries

48.5.1 Solid Organ Injury

Typical guidelines to determine which child needs an abdominal CT scan following accidental blunt abdominal trauma should not be applied to clinical situations where the goal is to identify occult abusive injury.

Diagnosing blunt abdominal trauma due to physical abuse is of particular importance to the critical care team because of the impact on the patient's morbidity and mortality. These injuries may be obvious based on the patient's clinical presentation or they may be occult. As with most cases of abusive trauma, the history provided frequently lacks a clear and accurate mechanism of injury. Abusive abdominal trauma is second only to AHT in mortality rates, with reports as high as 40–50%. For this reason, reducing delays in diagnosing occult blunt abdominal trauma is important. Case studies of children with abusive abdominal trauma demonstrate that the combination of abdominal bruising, tenderness or distention, or abnormal bowel sounds has a sensitivity of <60% for accurate diagnosis. Thus, relying solely on physical examination

will result in missing occult injury. Pediatric emergency medicine protocols for accidental blunt abdominal trauma utilize clinical findings (Glasgow Coma Score, pain, emesis, and evidence of thoracic abdominal wall trauma) and liver function and pancreatic enzyme levels to identify which child could benefit from additional evaluation such as an abdominal CT scan. It is important to point out that the goal of identifying which child can be observed following an accidental abdominal injury is very different from the goal of diagnosing occult blunt abdominal trauma due to abuse. Current child abuse literature supports using AST and ALT levels of >80 IU/L as screening tests to identify which patient should receive an abdominal CT scan to evaluate for occult blunt abdominal injury. Further, the receiver operator curves (ROC) for liver transaminases outperformed amylase and lipase in abusive abdominal trauma. Blunt trauma to the pancreas due to any mechanism may be more difficult to diagnose on initial presentation to medical care. Serial examinations and radiologic studies assist the diagnosis of blunt pancreatic injury. Finally, the use of bedside ultrasound to diagnose abdominal pathology in pediatric patients has now become the standard of care in many institutions, especially in the emergency department setting. The utility of identifying intra-abdominal free fluid or an abnormal finding that could indicate organ injury by a focused assessment with sonography for trauma (FAST) in combination with laboratory studies such as elevated liver transaminase and lipase contributes to screening tools for identifying which pediatric patients with an accidental trauma should receive an abdominal CT scan. To date however, there is no literature supporting the use of a FAST in diagnosing occult abdominal injury due to abuse. Currently, the gold standard for confirming a diagnosis of blunt abdominal trauma in a physical abuse evaluation is an abdominal CT scan.

48.5.2 Hollow Viscus Organ Injury

Viscus organ injury in pediatric patients described in the literature includes gastric perforation, duodenal hematomas, jejunoileal perforation, and mesenteric avulsions. These injuries are uncommon following accidental mechanisms, and due to their severity, they tend to be apparent on presentation to medical care. More subtle intestinal injuries are more challenging to diagnose in the absence of intraperitoneal fluid or air because screening tests for occult hollow viscus organ injuries are limited to those used for solid abdominal organ injury. Knowledge gained from lap belt injuries indicate that stricture formation at a point of blunt injury to the small intestine typically becomes apparent 2–4 weeks following the injury. Thus, placing a time course on abusive blunt intestinal injuries resulting in stricture formation can be challenging. For this reason, when a child presents with a clinical course of progressive intestinal obstruction due to stricture, blunt abdominal trauma due to physical abuse should be in the differential diagnosis so that an abuse evaluation can be completed as appropriate.

48.6 Protocolized Evaluation of Child Physical Abuse

To date, there has been a tremendous amount of research into individual aspects of the mechanisms of abusive injury and how to diagnose occult injuries. Thus, clinical tools derived from evidenced-based medicine direct diagnostic evaluations when visible injuries or clinical symptoms place physical abuse

Table 48.2 Fracture specificity for abusive mechanism of injury

Low specificity	High specificity
Clavicle fracture	Posterior rib fracture
Linear skull fractures	Metaphyseal long bone fracture
Long bone fracture	Scapula
Subperiosteal new bone formation	Sternal

in a differential diagnosis. These clinical tools are based on developmental age, mobility, and understanding mechanisms of injury. A skeletal survey is a radiologic tool used to identify occult fractures in children, typically <24 months of age, who present with bruising, burns, or another fracture concerning for physical abuse. The American Academy of Pediatrics and American College of Radiology have published statements recommending a skeletal survey be obtained on any child <24 months of age who has physical abuse in their differential diagnosis. While any fracture can be caused by either an abusive or an accidental mechanism, there are fracture locations and characteristics that are more specific for physical abuse (Table 48.2). Fractures with a "high specificity" for abuse can occur due to any trauma mechanism, but abuse is a common etiology. "Low specificity" fractures are those that are common with accidental injuries, but can also occur due to physical abuse. Posterior rib fractures, for example, are highly specific for abusive injury. Diagnosing a healing posterior rib fracture on a skeletal survey during a physical abuse evaluation may not significantly alter the medical management of the child, but it may help the care team identify an unsafe and potentially fatal environment. This is one powerful example of how care is supported by protocols that direct the use of adjunct tools such as a skeletal survey, head CT, retinal examination, and abdominal CT scan to diagnose physical abuse. Figure 48.10 is one example of an age- and evidenced-based medical approach to evaluating pediatric patients for physical abuse. An additional benefit of using such a protocol is removing caregiver bias from individual cases. Finally, the evaluation for occult injuries should be presented to the family as a trauma protocol rather than an option, due to the unknown risk of re-exposing a child to an unsafe environment.

48.7 Overdose and Self-Harm

Intentional self-harm and suicide attempt by drug overdose or other method may lead to admission to the ICU for close monitoring or lifesaving medical therapies. The most common physical sign of self-harm is cutting. Self-cutting is in general a non-suicidal self-injury behavior. Self-cutting is more common in young adolescent females than males. Self-injurious behaviors in adolescents are the visible signs of a complex interaction of several factors contributing to the mental health of the adolescent. These factors may include mental health illness, sociodemographic and educational factors, and adverse life events. Self-injurious behaviors can be a red flag for prior child physical and or sexual abuse. A team approach with social work, medical providers who are skilled in obtaining a history of abuse, and mental health providers can assist in identifying risk factors for the self-harm or suicide attempt. When there is a

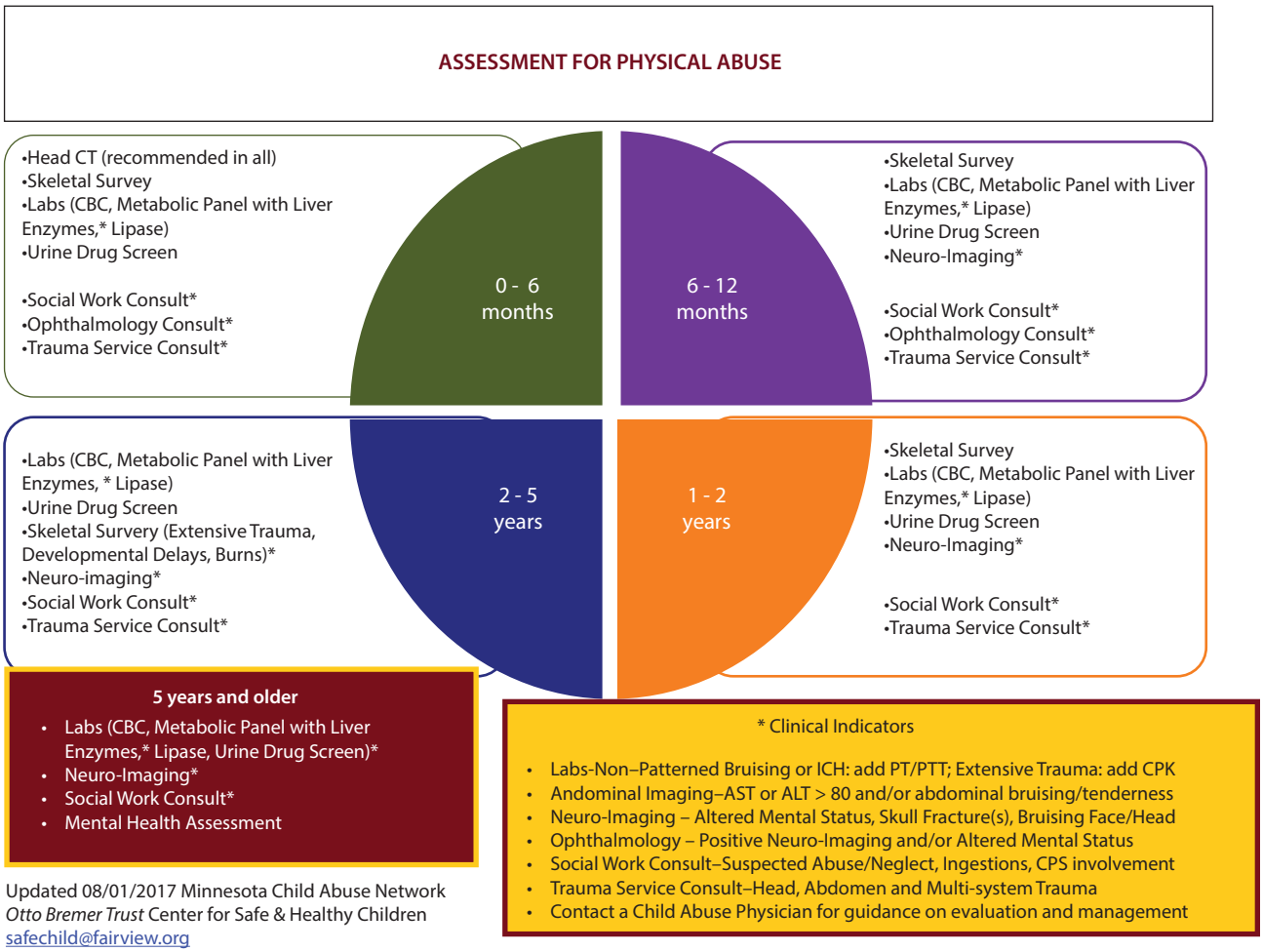

Fig. 48.10 Age-driven evaluation for physical abuse utilized by Fairview Health Services and Hennepin Healthcare Medical Systems. Our institution extends the TEN-4 FACES-p rule for infants up to 6 months of age. (Protocol chart designed and provided by Nancy Harper, MD)

concern for child sexual abuse, reporting to child protection services is necessary. How much a child is required to cooperate with this process, however, is dependent on his/her age and willingness to participate in the process. For example, an adolescent has the right to decline an examination and reporting to law enforcement for a sexual assault. Conversely, if there is disclosure of sexual abuse by a child under the age of consent by individual state law, this disclosure must be reported to law enforcement and child protection services as soon as possible. With any age patient, the medical team does have the responsibility to connect that patient to appropriate resources for medical care and mental health therapy.

48.8 Caregiver-Fabricated Illness in a Child

Caregiver-fabricated illness in a child frequently requires a team approach to diagnose this complex situation due to the false information presented to the medical team.

Caregiver-fabricated illness in a child is a type of child maltreatment that involves the provision of unnecessary and potentially harmful medical therapies or surgical interventions because the caregiver has falsified or induced symptoms of a medical condition. It can be described as a counterpart to medical neglect, and just as harmful. Traditionally, this type of child maltreatment was referred to in the literature as Munchausen syndrome by proxy and is still

referred to as medical child abuse. Caregiver-fabricated illness in a child is a preferred term since it focuses on the child as a victim of abuse rather than the motivation of the caregiver. This type of medical child abuse is frequently very difficult to diagnose for many reasons. Typically, the information provided to the medical team contains false information. The abused child may be medically complex with extensive evaluations by many caregivers within and between medical care systems. The critical care team may unwittingly be a part of the maltreatment when the child presents following surgical intervention or with unexplained illness. The presenting symptoms cover broad diagnostic areas for which care is provided in a PICU. These include anaphylaxis or allergies, endocrine and metabolic alterations such as hypoglycemia, gastrointestinal symptoms that include hematemesis and hematochezia, anorexia and feeding difficulties, infections with uncommon microflora, and acute respiratory symptoms such as apnea and brief resolved unexplained events. Intoxications with ethanol, laxatives, and sedatives are commonly reported in these complex cases.

With such a complex and evasive medical diagnosis, optimal care provided by the medical team for victims of caregiver-fabricated illness is more successful when a multidisciplinary team approach is taken. It is imperative that the team approach includes all care providers, most importantly the primary care provider. The medical team should address the following questions: (1) Are the signs and symptoms of the illness credible and have they been observed/documented by medical providers? (2) Does the child require medical interventions that are harmful if they are not medically necessary? (3) Who is asking for the medical interventions or evaluations? Review of the patient's condition and therapy by all providers, including a child abuse pediatrician, may lead to a report to child protection services for additional support. The need for covert video surveillance is very infrequent and does require supervision by the hospital legal department. An optimal long-term outcome of these cases occurs when the offending caregiver is capable of admitting to the harm caused and can be a part of the healing process. The obvious concern is risk for re-injury, which may occur if the child is returned to the offending caregiver without a safety plan and interventions put into place.

48.9 Mandated Reporting

All medical providers are mandatory reporters of child abuse and maltreatment.

In suspected child physical abuse, detailed documentation in the medical record is of paramount importance. The history of presenting illness should be paraphrased from caregivers during the initial history intake. A documented complete developmental history clarifies the physical ability of the patient. Identification and clear diagnoses of cutaneous findings as bruising, hematoma, petechiae, etc. should be entered into the medical record. Many electronic medical record systems have drawing tools to embed the location of and measurements of cutaneous findings within a provider note. The addition of photo documentation is strongly encouraged to aid in communication between medical providers, to follow healing, and to help differentiate bruises from other conditions (e.g., congenital dermal melanocytosis). Photo documentation is most helpful when performed by those skilled in these techniques. Where photo documentation should be stored is at the discretion of each institution's child abuse and legal teams. Finally, multidisciplinary team meetings are encouraged so that consistent terminology and diagnoses are communicated in the medical record. The medical record documentation may be requested by child protection services and law enforcement when a case is reported. All medical professionals are mandatory reporters when child maltreatment is in the differential

diagnosis or a contributing factor to the child's condition. A verbal report to child protection services should be made as soon as possible once the medical team concludes maltreatment may have contributed to the child's condition. A written report typically is required to support the verbal report. One reason for the urgency to report concerns for child abuse and neglect is that other vulnerable individuals within the home or child care setting may be at risk for harm. There may be perceived conflict of interest when physicians caring for the child make a report to child protection services. On the contrary, critical care physicians have some of the most difficult conversations with families, and reporting to child protection should be no different. One approach to help bridge this difficult situation is to state to the patient's guardians that all care providers are mandatory reporters and all children with the findings at hand require consultation with child protection services. It is helpful to also state that the medical team will provide ongoing support to the family during this stressful time.

Critical care physicians and allied providers have varying degrees of comfort working with investigators and attorneys. It is helpful to remember that you are experts in critical care medicine and part of your responsibility is to educate others. Related to this point is the clarity of the medical decisions and findings within the medical record. Occasionally, critical care physicians may find themselves consulted by child protection and law enforcement or subpoenaed by a family or district court. In these situations, the critical care physician may be asked to assist in the investigation of possible child maltreatment by providing education about the child's medical condition and diagnosis. There are two types of court before which a physician is typically called to testify. District court is a part of the federal court system that hears cases of physical abuse and sexual abuse. Family court, governed by state or local laws, hears cases of child custody. Most often, the critical care physicians testify in court because they are "fact" witnesses. As a fact witness, you are the critical care expert teaching the court what medical findings and diagnoses mean with respect to your patient in a factual manner. "Expert" witnesses are experts in their specific field that are asked to testify in court more broadly about their area of expertise with respect to the patient. For example, an expert in coagulation abnormalities who may or may not have cared for the patient can be asked to testify in court due to their area of expertise. Key points on successfully testifying in court are: (1) know your educational background and what makes you an expert in critical care medicine, (2) know your patient and what role you had in caring for the patient, and (3) be able to explain to lay people the medical condition you were treating. If asked to render an opinion in an area in which you are not an expert, it is appropriate to state just that. Many times a child abuse pediatrician will testify in cases of, for example, AHT that results in death. In this scenario, the critical care physician is an expert in TBI and pronouncing brain death, and AHT is a subset of TBI. The child abuse pediatrician is an expert in AHT and can discuss the literature supporting how the diagnosis of AHT is made. Before going to court, it is always appropriate to review what to expect in court with the attorney who initiated the subpoena. Your institution's legal office can also be a resource.

Review Questions

1. The repetitive rotational mechanism of abusive head trauma as seen with vigorous shaking in a 3-month-old is least commonly associated with which clinical finding:
   A. Apnea
   B. Retinal hemorrhages
   C. Cervical spine fractures
   D. A worse outcome when compared to accidental traumatic brain injury
   E. Cervical spine ligamentous injury

2. The clinical signs consistent with blunt contact forces to the head include:
   A. Parietal bone fracture
   B. Subdural hemorrhage
   C. Scalp hematoma
   D. All of the above

3. A 10-month-old infant is admitted to the PICU after a second episode of respiratory failure requiring mouth-to-mouth resuscitation by the infant's mother. Per the patient's mother, the infant also has an extensive history of bright red blood per rectum. The electronic medical record demonstrates the infant has been seen in numerous clinics for evaluation of allergies causing the bleeding symptoms and several formula changes have been recommended. On evaluation of the child, you find a healthy infant with no respiratory distress, a benign abdominal examination, and a normal anus and rectum on external examination. The next best step in this child's medical evaluation is:
   A. Make a report to child protection services with concerns for medical neglect based on likelihood the mother is not providing the recommended protein hydrolysate formula resulting in repeated hospital admissions.
   B. Start an evaluation for allergic colitis that includes a CBC with differential, serum IgE level, and gastroenterology consultation.
   C. Convene a multidisciplinary meeting of all representative care providers including the primary care physician to review what symptoms have been observed by medical providers and if the recommended medical interventions have affected the child's symptoms.
   D. Since the two episodes of mouth-to-mouth resuscitation implies there is an underlying life-threatening cause of these brief resolved unexplained events (formerly known as apparent life-threatening event), a 24-hour ambulatory electrocardiography device should be placed prior to discharge.

4. Plan an ideal timeline for evaluating a 6-month-old child with suspected physical abuse due to facial and leg bruises and vomiting:
   A. Head CT on admission, liver transaminases on admission, skeletal survey within 48 hour of admission, and brain and spine MRI within 48 hours of admission if head CT is abnormal
   B. Liver transaminases on admission, head CT 24 hours after admission, ophthalmologic examination 24 hours after admission, and skeletal survey within 48 hours of admission
   C. Skeletal survey within 48 hours of admission, liver transaminases on admission, head CT on admission, and brain and spine MRI 1 week after admission if the head CT is abnormal
   D. Skeletal survey on admission, abdominal ultrasound on admission, liver transaminases 24 hours after admission, and head CT on admission

5. A 5-month-old female is evaluated in the emergency department for emesis and fever. There is a faint pink rash on the infant's abdomen. On physical examination, the infant has slight rhinorrhea and a healing torn upper labial frenulum, and she is observed to be well hydrated. Despite having private medical insurance, the parents express concern about the impact this emergency department visit will have on their family. Failing to place physical abuse in the differential diagnosis of a healing frenulum due to no "red flags" in the observed social situation is most consistent with:
   A. A gap in knowledge that a labial frenulum injury may be due to physical abuse

B. Misconception that the torn frenulum can appear like oral lesions consistent with a viral infection
C. Preconceived bias that physical abuse cannot happen in a family with no socioeconomic red flags
D. Being concerned that a physical abuse evaluation would upset a family with no "red flags" and cause them not to return for medical care

6. A 4-month-old infant was found unresponsive and not breathing at daycare. The emergency medical response team performed CPR for 30 min, and after two doses of epinephrine, return of spontaneous circulation was achieved. Due to concerns that the infant may have suffered life-threatening abusive head trauma, a child abuse evaluation was performed. Choose the most correct statement about the retinal hemorrhages in this scenario?
A. Retinal hemorrhages due to the birth process are likely to still be present.
B. Retinal hemorrhages due to CPR are likely in this scenario to be described as "too numerous to count" and extend out to the ora serrata in both eyes.
C. CPR would not be associated with retinal hemorrhages in this scenario because there was return of spontaneous circulation.
D. Less than 20 retinal hemorrhages around the posterior pole of one eye could be due to either CPR or diffuse forces associated with AHT.

Answers

1. C
2. D
3. C
4. A
5. C
6. D

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Palliative Care in Pediatric Critical Care

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Contents

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Learning Objectives

- To understand the epidemiology of pediatric death and its relevance to the practice of pediatric critical care medicine
- To understand the determination of cardiopulmonary death in children
- To recognize and effectively address the physical, psychosocial, spiritual and environmental needs of the patient and his or her family
- To appreciate the many ethical issues relevant to end-of-life care in children including the Doctrine of Double Effect
- To define bereavement and understand its impact on health outcomes
- To recognize the potential role of the pediatric critical care provider in family bereavement after the death of a child

49.1 Introduction: Epidemiology of Pediatric Death

The field of pediatric palliative care has grown substantially since first recognized as a subspecialty by the American Board of Medical Specialties in 2006. Although there is a trend toward increasing pediatric deaths outside of the hospital setting, several recent publications have demonstrated that the pediatric intensive care unit (PICU) is still the most common location of pediatric death. Thus, this expansion of pediatric palliative care has clear implications for pediatric critical care medicine practitioners, and a sound understanding of the basic tenets of this practice is essential.

Mortality rates among pediatric intensive care unit admissions have decreased over time. Four recent multicenter studies have reported PICU mortality rates less than 3%.

Encouragingly, pediatric mortality appears to be decreasing in the United States. Data from the Centers for Disease Control and Prevention reveal that there were 32,709 reported deaths among infants and children less than 15 years of age in the United States in 2016. In contrast, that number was nearly double in 1980 when there were 64,402 reported deaths among this age group. Figure 49.1 illustrates the progressive decrease in mortality rates among three pediatric age groups since 1950. Interestingly, for children 1 to 14 years of age, the mortality rates have remained relatively stable since 2010. Mortality rates

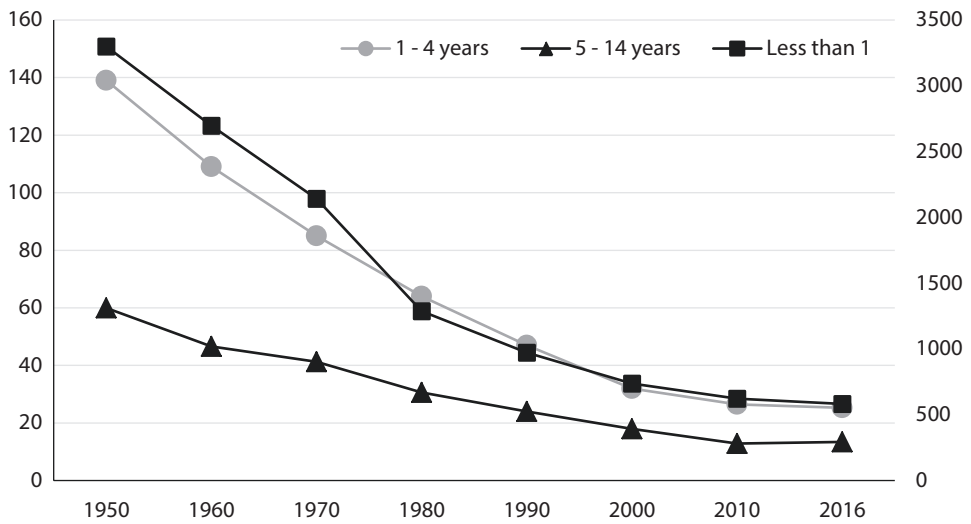

Fig. 49.1 Mortality rates among three pediatric cohorts for all causes in the United States from 1950 through 2016. The figure depicts the decreasing mortality rates among three pediatric cohorts from 1950 through 2010 with relatively stable rates since then. The less than 1 year of age cohort (solid black squares, solid black line) is plotted on the right-sided secondary axis. The 1- to 4-year-old cohort (gray circles, gray line) and the 5- to 14-year-old cohorts are plotted on the left-sided, primary axis. Mortality rates are expressed in deaths per 100,000 resident population. (Data from National Center for Health Statistics. Health, United States, 2017: With Special Feature on Mortality. Hyattsville, MD. 2017. Data Finder: Table 21. Death rates for all causes, by sex, race, Hispanic origin, and age: United States, selected years 1950–2016)

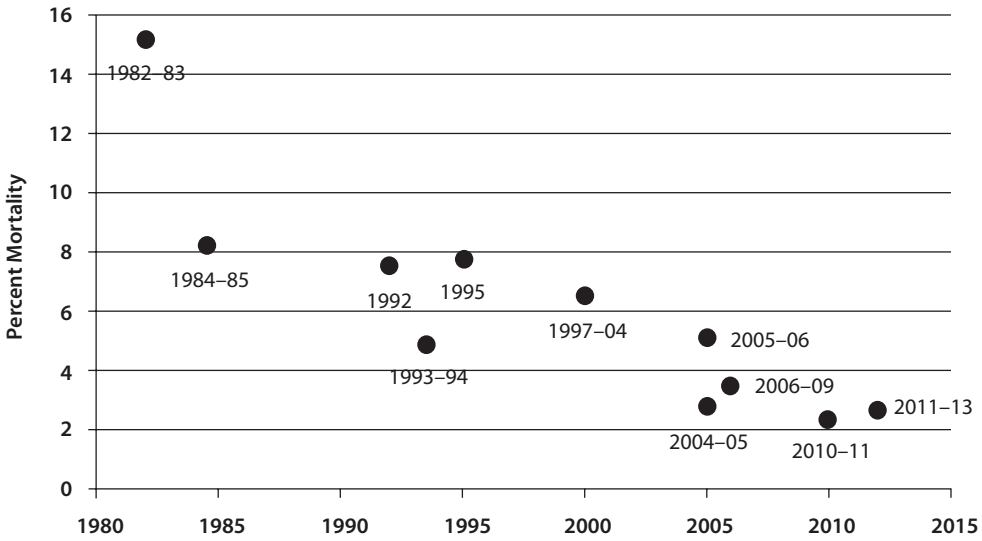

Fig. 49.2 Mortality rates among pediatric intensive care unit admissions over time. This figure illustrates the declining rates of mortality in the pediatric intensive care unit over the past three decades. The years next to each data point indicate the years that the data were collected. The y-axis represents the percent mortality. (Copied with permission from: Suttle ML, Jenkins TL, Tamburro RF. End-of-Life and Bereavement Care in Pediatric Intensive Care Units. Pediatr Clin North Am. 2017;64:1167–83)

among PICU admissions have also decreased over time (Fig. 49.2). Four recent multicenter studies have reported PICU mortality rates less than 3%.

Despite the decreasing overall mortality, and the decreasing PICU associated mortality, recent publications as described above suggest that the PICU remains the most common location of childhood death in the United States. Prospective, multicenter data suggest that the withdrawal or the withholding of life-sustaining therapies accounts for 70% of PICU patient deaths. The remaining 30% are fairly equally divided between a diagnosis of brain death (16%) and failed cardiopulmonary resuscitation (14%). One recent publication of over 15,000 deaths included in the Virtual Pediatric Systems national database reported that brain death accounted for approximately 20% of these deaths. In light of these findings, it is not surprising that most children who die in the PICU have a resuscitation plan discussed and established. In addition, palliative care consultation for these children appears to be common and increasing over time.

The PICU remains the most common location of childhood death in the United States.

Prospective, multicenter data suggest that approximately 70% of patients dying in a PICU do so in the context of withdrawal or withholding of life-sustaining therapies with the remaining 30% fairly equally divided between a diagnosis of brain death and failed cardiopulmonary resuscitation.

In terms of causes of death, congenital malformations/chromosomal abnormalities and disorders related to prematurity remain the most common cause of death in children under 1 year of age, while unintentional injury is the leading cause of death in children 1 year and older. Within the PICU, multiple organ failure has been reported to be the most common diagnosis at the time of death followed by neurologic and respiratory disorders. Burns reported that PICU deaths can be characterized into one of two groups based on their PICU length of stay at the time of death. In that study, children who died within a week of PICU admission were more likely to be diagnosed with a new, acute illness or injury (both unintentional and intentional) and were more likely to die as a result of brain death or failed resuscitation. Those who died after a week into their PICU course were characterized by preexisting conditions and prior technology dependence; their deaths were more likely to occur in the setting of the withdrawal of life-sustaining support.

Unintentional injury is the leading cause of death in children 1 year and older.

Although injuries and acute illness are prevalent causes of deaths in the PICU, most deaths in the PICU are associated with a preexisting or chronic condition. Feudtner has defined a pediatric complex chronic condition as “any medical condition that can be reasonably expected to last at least 12 months (unless death intervenes) and to involve either several different organ systems or one organ system severely enough to require specialty pediatric care and probably some period of hospitalization in a tertiary care center.” Utilizing

Although injuries and acute illness are prevalent causes of deaths in the PICU, most deaths in the PICU are associated with a preexisting or chronic condition.

such a definition, large-scale data suggest that a slight majority of the children admitted to a PICU have a complex chronic medical condition. Moreover, these same data suggest that these children account for nearly three quarters of PICU mortality.

The American Academy of Pediatrics and the Institute of Medicine have long recommended that palliative care should be initiated at the time of diagnosis of a life-limiting condition and be implemented concurrently with curative therapies.

The findings that children with complex chronic conditions account for both a large proportion of PICU admissions and PICU mortality support the need for effective palliative care within that setting. Both the American Academy of Pediatrics and the Institute of Medicine have long recommended that palliative care should be initiated at the time of diagnosis of a life-limiting condition and be implemented concurrently with curative therapies.

The 2010 Patient Protection and Affordable Care Act [2010 (Pub L No.111-148)] indicated that children can concurrently receive hospice services and curative or life-extending therapy.

Additionally, the 2010 Patient Protection and Affordable Care Act [2010 (Pub L No.111-148)] indicated that children can concurrently receive hospice services and curative or life-extending therapy. Thus, palliative care services should not only be provided at the end of life for these children, but rather, provided from the time of diagnosis and throughout their frequent admissions to the hospital and intensive care unit. Given that data suggest children discharged from the PICU with palliative care services in place are more likely to die outside of the hospital, the initiation of palliative care early in the course of these complex chronic conditions holds the potential to improve care and quality of life for these children and their families.

49.2 Definitions of Death

49.2.1 The Determination of Cardiopulmonary Death

The Dead Donor Rule prohibits the transplantation of vital organs until after the donor has been declared dead and also states that living subjects must not be killed by organ retrieval.

The determination of cardiopulmonary death may at first seem straightforward in comparison to that of brain death. However, the use of this determination has become increasingly more complex alongside the expansion of organ donation programs across the United States. Donation after cardiac death (DCD) protocols prohibit the transplantation of vital organs until after the donor has been declared dead, thus, upholding the "Dead Donor Rule" which was established by the Uniform Determination of Death Act (UDDA) in 1981. The Dead Donor Rule further states that living subjects must not be killed by organ retrieval, thus necessitating a means of identifying the exact moment of death.

In the 1990s, the University of Pittsburgh protocol established that donors could be declared dead after 2 minutes of asystole or apnea. Since that time, numerous medical societies and experts have issued guidelines with variations on how long a donor or patient must have asystole or apnea to be declared dead. The Ethics Committee of the Society of Critical Care Medicine requires 2–5 minutes, whereas the US Institute of Medicine requires 5 minutes.

Autoresuscitation is the phenomenon of the heart being able to restart spontaneously and generate anterograde flow. The longest duration of autoresuscitation reported in pediatrics is 2 minutes, following failed CPR.

A topic that often complicates the determination of cardiopulmonary death, particularly the duration of asystole or apnea required, is that of autoresuscitation or the phenomenon of the heart being able to restart spontaneously and generate anterograde flow. Hornby published a review of autoresuscitation in which their group found cases of up to 65 seconds of pulseless electrical activity (PEA), but no cases of autoresuscitation leading to restored circulation after withdrawal of life-sustaining treatments. However, in situations of failed cardiopulmonary resuscitation (CPR), the review did find 32 cases of autoresuscitation leading to restored circulation up to an interval of *7* minutes (one case) after asystole began. This early review did not include children, but

the group's recent update does include four studies with pediatric patients. The longest event of autoresuscitation reported in a child following failed CPR was 2 minutes and 10 minutes for one adult.

In contrast, there were no reported cases of autoresuscitation in 12 pediatric patients studied following withdrawal of life-sustaining treatments. Six adults experienced autoresuscitative events following withdrawal of life-sustaining treatments, with the longest event being 89 seconds. It should be noted that all the pediatric patients with autoresuscitative events died, while eight adults from the prior review and three from the update recovered fully.

To standardize practice among medical providers, an invitational forum sponsored by Health Canada and Canadian Blood Services in collaboration with the World Health Organization (WHO) was held in Montreal, Canada, in 2012 to start the process of developing international guidelines for the determination of death. The forum consisted of experts representing a broad range of national and international professional societies involved with death determination in adults and children in acute care settings. Based upon current evidence, practice, and expert opinion, this Committee agreed that mechanical asystole (i.e., absence of a heartbeat upon auscultation or loss of palpated pulse) and apnea for a duration of 2–5 minutes in situations of withdrawal of care and a duration of 2–10 minutes in situations of failed CPR is an acceptable practice.

Mechanical asystole and apnea for a duration of 2–5 minutes in situations of withdrawal of care, and a duration of 2–10 minutes in situations of failed CPR, is an acceptable practice for determining cardiopulmonary death in pediatrics.

49.2.2 Brain Death Determination

The determination of brain death is described in detail in ▶ Chap. 24 "Assessment of Neurologic Function."

49.3 End-of-Life Care in the PICU

Quality end-of-life (EOL) care in the PICU remains an essential component of any successful pediatric critical care program, yet the successful integration of multidisciplinary palliative medicine into routine care remains a challenge in pediatrics. Comprehensive and time-intensive care may be particularly challenging for the critical care provider, who is confronted with simultaneously caring for other critically ill children with much more promising prognoses. Evidence would suggest that wide variability exists with regard to identifying and addressing the complex issues associated with EOL care in the PICU.

Beyond the ever important treatment of physical suffering, effective palliative care must also address the child's psychosocial and spiritual needs, as well as provide support to the family as a whole; clearly critical illness effects the entire family and has the potential for long-standing dysfunction for surviving family members. Pediatric critical care clinicians of all disciplines must strive to develop a sound understanding of EOL care and its potential to impact the quality of life for patients, families, and even healthcare providers.

49.3.1 Physical Needs

Evidence would suggest that most pediatric critical care providers express confidence in their ability to treat the acute symptoms of the dying patient including pain, agitation, dyspnea, secretions, and seizures. However, they appear less comfortable in their ability to treat more chronic issues such as skin breakdown and

constipation. Although little is published regarding the personal priorities of children nearing death, adult patients have consistently reported pain and other symptom management as a high priority of EOL care. For parents facing the loss of their child, the relief of their child's pain and suffering is a critically important need. However, and discouragingly, bereaved family members have historically reported poor management of distressful symptoms. PICU clinicians should begin the process of symptom management by first educating families of the anticipated physical symptoms associated with EOL and the potential therapies for these symptoms. Parents should be given a platform to express their concerns and to identify their unique preferences. They should be provided with reassurance that relieving their child's pain and suffering is a top priority of the care team. Clinical practice guidelines to manage EOL symptoms in children with cancer have been developed and would appear appropriate for use in children with other life-threatening conditions (Tables 49.1 and 49.2).

Despite effective and ever-improving therapies, there are still rare situations where children will experience intractable and intolerable physical suffering at the EOL. In such difficult situations, the use of palliative sedation may be the only manner in which unrelenting pain and distress may be addressed. This therapy, however, must be reserved for truly only those situations where all other more standard EOL care and aggressive pain management strategies prove ineffective. Palliative sedation therapy attempts to relieve intolerable and refractory suffering by reducing patient awareness, even to the point of unconsciousness. It has the single goal of assuring comfort. It should only be used when the healthcare team and the family are in complete agreement that the child is imminently dying and experiencing refractory and intolerable symptoms. Its goal is not to hasten death, but only to alleviate refractory physical suffering (see Doctrine of Double Effect).

Ketamine may alleviate severe pain and decrease the use and escalation of opioids at EOL. It may also effectively treat neuropathic pain. Dexmedetomidine can be used in combination with pain regimens to reduce agitation and decrease pain scores.

Many medications have been used for palliative sedation therapy including benzodiazepines, propofol, barbiturates, opioids, and antipsychotics at doses that achieve continuous deep sedation. However, more focused data and study are needed in children. Propofol has long been suggested as an effective medication for terminal sedation, and a small case series of its use for palliative sedation found it to be effective in children dying of cancer. Additionally, ketamine and dexmedetomidine have been observed to hold promise in treating refractory pain and distress at EOL for children. Ketamine has been reported to alleviate severe pain and decrease the use and escalation of opioids at EOL in both adults and children with cancer. In the pediatric cases, Conway reported that bolus doses ranged from 0.1 to 0.24 mg/kg/dose and infusion rates from 0.05 to 4.1 mg/kg/hour. Important to note, and in contrast to palliative sedation, patients were noted to be awake and interactive with family members at doses as high as 1.7 mg/kg/hour. Ketamine also appears to be an effective treatment for neuropathic pain in children at EOL. In one study, Taylor reported that the median initial continuous infusion dose of ketamine to treat neuropathic pain was 0.06 mg/kg/hour with an average dose needed of 0.08 mg/kg/hour and a range of 0.014–0.308 mg/kg/hour. The majority of patients required doses below 0.1 mg/kg/hour, and the maximum continuous infusion dose required to relieve neuropathic pain was 0.308 mg/kg/hour. Dexmedetomidine, an α2-adrenoreceptor agonist, has been evaluated as an adjuvant therapy to treat pain and agitation in children and adolescents with advanced illness at EOL. Burns observed a significant decrease in pain scores after the initiation of a dexmedetomidine infusion using a bolus dose of 1 mcg/kg/dose administered over 10 minutes, followed by a continuous infusion at 0.1–3 mcg/kg/hour. In that report, bolus doses of 0.1 mcg/kg/dose were subsequently administered up to every 30 minutes if pain scores remained elevated.

In addition to pharmacologic methods, the pediatric critical care provider should have a working knowledge of non-pharmacologic therapies of control-

Table 49.1 Pediatric symptom management (non-pain) at the end of life

Symptom	Medication	Common pediatric dosage (<60 kg)[1]	Maximum dose[1, a]
Agitation/ delirium	Non-pharmacologic	Familiar objects, low lighting, soothing tones/music	NA
	Lorazepam	0.05 mg/kg/dose PO, PR, or SL/IV (preferred for seizure) every 4–6 h	2 mg per dose
	Chloral hydrate	25–50 mg/kg/day PO/PR divided every 6–8 h	1 g/day for infants, 2 g/day for children
	Haloperidol	0.01–0.02 mg/kg/dose PO, SL, IV or PR every 8–12 h	0.15 mg/kg/ day
Dyspnea	Non-pharmacologic	Elevate head of bed, suctioning, fluid restriction, bedside fan, flowing air	NA
	Morphine	0.15 mg/kg/dose PO/SL or 0.05 mg/ kg/dose IV every 2 h PRN (titrate to effect)	As limited by side effects
	Lorazepam[b]	0.05 mg/kg/dose PO/SL/IV every 4–6 h PRN (titrate to effect)	2 mg per dose
Nausea/ vomiting	Non-pharmacologic	Avoid irritating foods or smells, relaxation, biofeedback, acupuncture, aromatherapy	NA
	Ondansetron	0.15 mg/kg/dose PO/IV every 8 h PRN	8 mg per dose
	Promethazine	>2 y: 0.25 mg/kg/dose PO/IV every 6–8 h PRN	1 mg/kg/day
	Scopolamine	8–15 kg, half patch TD every 3 days; >15 kg, 1 patch TD every 3 days	1 patch every 3 days
	Metoclopramide	0.01–0.02 mg/kg/dose per dose IV every 4 h	
	Lorazepam	0.05 mg/kg/dose PO/SL/IV every 4–6 h (PRN) titrate to effect	2 mg per dose
Secretions	Non-pharmacologic	Fluid restriction, gentle suctioning	NA
	Glycopyrrolate	0.04–0.1 mg/kg/dose PO every 4–8 h 0.01–0.02 mg/kg/dose IV every 4–6 h	1–2 mg per dose or 8 mg/day PO

Adapted from Johnson L-M, Snaman JM, Cupit MC, Baker JN. End-of-Life Care for Hospitalized Children. Pediatr Clin N Am. 2014;61:835–54

NA not applicable, *PO* by mouth, *PR* per rectum, *h* hour, *SL* sublingual, *IV* intravenous, *TD*,Transdermal

[a]Common maximum dosage; however, dose escalation may be necessary at EOL

[b]Lorazepam used for dyspnea associated with anxiety

[1]The dosages provided are general guidelines, but should be verified with a pharmacist, palliative care specialist or other appropriate resource prior to administering to any individual patient

ling pain and distress at EOL. For example, the use of a fan to provide a steady stream of cool air to the face has been found to effectively reduce the discomfort associated with terminal air hunger. In Europe, a hand-held fan is now an established component of the Breathlessness Support Service which aims to

Table 49.2 Pharmacologic management of pediatric pain at the end of life

Drug	Initial dose[1]	Route	Interval	Maximum dose[1]
Acetaminophen	10–16 mg/kg	PO/PR/IV	q 4 h	1 g/dose 4 g/day
Ibuprofen	5–10 mg/kg	PO	q 6 h	2.4 g/day 3.4 g/day (adults)
Naproxen	5–7 mg/kg	PO	q 8–12 h	1 g/dose 4 g/day
Ketorolac	0.5 mg/kg	PO, IV	q 6 h	30 mg/dose (IV) 10 mg/dose (PO)
Tramadol	1–2 mg/kg	PO	q 6 h	100 mg/dose 400 mg/day
Morphine	0.2–0.5 mg/kg 0.1 mg/kg 0.3–0.6 mg/kg (LA)	PO, SL, PR IV, SQ PO	q 3–4 h q 2–4 h q 8–12 h	Titrate
Hydromorphone	0.03–0.08 mg/kg 0.015 mg/kg	PO, PR IV, SQ	q 3–4 h q 2–4 h	Titrate
Methadone	0.2 mg/kg 0.1 mg/kg	PO IV, SQ	q 8–12 h q 8–12 h	Titrate
Fentanyl	0.5–1 μg/kg/h 5–15 μg/kg (sed) 1–2 μg/kg	TD TM IV, SQ	q 48–72 h q 4–6 h q 1–2 h	Titrate
Oxycodone	0.05–0.15 mg/kg 0.1–0.3 mg/kg (LA)	PO PO	q 6 h q 12 h	Titrate

PO by mouth, *PR* per rectum, *IV* intravenous, *SL* sublingual, *SQ* Subcutaneous, *LA* Long acting, *TD* transdermal, *sed* sedative, *TM* transmucosal

[1]The dosages provided are general guidelines, but should be verified with a pharmacist, palliative care specialist or other appropriate resource prior to administering to any individual patient

Adapted from Johnson L-M, Snaman JM, Cupit MC, Baker JN. End-of-Life Care for Hospitalized Children. Pediatr Clin N Am. 2014;61:835–854

relieve dyspnea among the chronically ill. Other non-pharmacologic therapies including acupuncture, massage, and transcutaneous electrical nerve stimulation may provide comfort and relief of physical suffering. Additionally, music therapy, art therapy, pet therapy, organic supplementation, and faith healing may all be of potential benefit at the end of life. In one study of 96 children who died of cancer, nearly one third of parents reported using at least one form of such complementary and alternative medicine (CAM) interventions. Moreover, nearly 80% of these parents offered that these therapies benefited their dying child with most reporting no additional suffering. Not surprisingly, the authors also noted that there was increased use of CAM therapies when the physician engaged in open dialog with the families regarding their use.

49.3.2 Psychosocial Needs

Children may experience distress at EOL due to loss of control over their bodies, loss of personal identity, and loss of interpersonal relationships. This distress may present as anxiety and/or depression.

Although many pediatric patients facing death in the PICU may be sedated or neuro-cognitively impaired from critical illness, some children may still exhibit psychosocial distress linked to various illness related factors. A child's reaction to illness and their understanding of the concept of death is largely influenced by their cognitive and developmental level. Published experiences suggest that

there are three losses that cause the most distress for children: (1) loss of control over their bodies and what is happening at any given moment, (2) loss of personal identity, and (3) loss of interpersonal relationships. This distress can often manifest as both anxiety and depression. Thus, determining the extent to which each of these losses is affecting a dying child may prove invaluable in effectively meeting their emotional needs and those of their family. Collaboration with psychology and/or psychiatry teams may be useful.

Medical providers should strive to provide EOL care that is inclusive of a family's personal, cultural, religious, and spiritual beliefs. Spirituality appears to play a significant role in adult grief reactions. Therefore, understanding a family's religious or spiritual foundation and facilitating the expression of those beliefs may provide comfort and a sense of meaning for surviving family members as a child approaches death. Hospital chaplains may play an important role in helping clinicians identify and honor the specific religious and spiritual needs of families.

One of the most prominent spiritual needs described by bereaved parents is that of maintaining a connection to their child at the EOL. Clinicians may foster this connection by helping parents maintain the parent-child relationship at EOL. As parents struggle with the loss of their traditional roles of protector and provider, maintenance of the parent-child relationship may be facilitated by encouraging active parent involvement in patient care, allowing parents to be present during invasive procedures and/or cardiopulmonary resuscitation, providing the opportunity to stay with their child at the time of death, and helping parents create memories that can bring comfort in the future.

At the end of a child's life, parents desire to maintain a connection to their child. Clinicians can support this desire by maintaining the parent-child relationship and encouraging parents to be involved in patient care, allowing parental presence for procedures, and helping parents create memories of their child.

Parents also need staff to be kind, compassionate, understanding, and patient. They want to know that the medical team genuinely cares about their child. Although clinicians previously unknown to the family may be quickly incorporated into the parents' support network, special effort should be made to include extended family and friends during the EOL process (if so desired by the parents). This effort may facilitate continuity of support when the child dies and the parental support network abruptly shifts from the medical team to primarily family members and friends.

49.3.3 Environmental Needs

Medical providers should also maintain awareness of a family's environmental needs at EOL. Bereaved parents have reported that memories of a welcoming environment can contribute to comfort during bereavement, while environmental frustrations may lead to negative interpersonal interactions and greater grief for parents.

A welcoming environment for families can provide comfort to parents during bereavement, whereas environmental frustrations can lead to greater grief.

Environmental needs include easy access to their child, privacy, facilities for self and sibling care, and the ability to accommodate family and friends at the time of death. Although always a challenge to accommodate within the busy setting of a PICU, developing a plan that all caregivers will follow to meet the environmental needs of a dying child and their family may enhance the quality of EOL care, improve family satisfaction with care, and create an atmosphere that facilitates interaction and support. If medically feasible, transferring the child to a private room in a more remote section of the PICU will often help in providing such an environment while at the same time minimizing disruption to the normal work flow of the unit.

49.3.4 Communication

Communication is a key component to quality end-of-life care. Parents desire honest communication that is given in a caring manner, using simple language. Parent-physician interactions that use more empathetic statements, emotional talk, and time for questions lead to improved parental satisfaction with care.

Communication at the EOL is a vital component to addressing the needs of families. Multiple studies have reported a parental need to receive *honest* communication that is given in a compassionate, unhurried, and sensitive tone. Honest communication for parents includes frequent updates on their child's condition and prognosis, which is needed for complex decision-making. Such honest communication has been reported to enhance parental understanding and reduce conflict. In contrast, evasive answers and incomplete information have been noted to undermine trust and negatively impact the parents' ability to cope with the death of their child. Parents of dying children also desire simple language rather than medical jargon. Parent-physician interactions with patient-centered elements, such as increased proportions of empathetic statements, question asking, and attention to emotional needs, positively influence parent satisfaction with care independent of the child's severity of illness. High-quality communication at the end of a child's life fosters trust between families and medical staff and helps to ensure that dying children receive the best possible care.

Clinicians may be asked to facilitate communication about death between parents and their dying child. These conversations should be done in series, with content specific to the child's cognitive level, and may utilize various methods such as writing or artwork.

In some cases, clinicians may be tasked with helping to facilitate communication about death between parents and their dying child. These discussions may be pivotal in helping families work through this most difficult of situations. In a large study, Kreicbergs et al. found that among parents who elected to discuss death with their dying child (n = 147), *all* reported satisfaction with their decision. In contrast, more than a quarter (69 of 258, 27%) of those who chose not to have this discussion were dissatisfied with their decision. The content and approach to these conversations will depend upon the developmental level of the child and, in addition to talking, may also occur via writing, drawing, or other forms of communication. These "discussions" are usually most effective when they occur in series. It is widely contended that providing dying children the opportunity to openly discuss death, grief, and illness minimizes their confusion and fears. In addition to palliative care medicine, other services such as Psychology and Child Life can be extremely helpful in explaining concepts of death in developmentally appropriate ways to patients and their siblings.

49.4 Ethical Issues

As described above, approximately 70% of patients dying in a PICU do so in the context of withdrawal or withholding of life-sustaining therapies. Thus, most children who die in the PICU, and perhaps others who do not, have a resuscitation plan established. The foundation of such a plan, and usually the initiation of such a plan, is focused on the withholding of cardiopulmonary resuscitation.

Although seemingly straightforward, there is often confusion between the actual intent of the Do-Not-Resuscitate (DNR) order and the interpretation by the healthcare team.

A Do-Not-Attempt-Resuscitation (DNAR) (more commonly referred to as a Do-Not-Resuscitate (DNR)) order, in its most fundamental form, states that cardiopulmonary resuscitation will not be initiated in the event of cardiopulmonary arrest. The implementation of pediatric palliative care programs has been associated with an increase in the number of DNR orders written in published reports. Although seemingly straightforward, there is often confusion between the actual intent of the order and the interpretation by the healthcare team. Sanderson assessed the meaning, implication, and timing of DNR orders for critically ill children among 266 physicians (n = 107) and nurses (n = 159). She reported that two thirds of the clinicians surveyed believed that a DNR order only limits care in the event of cardiopulmonary arrest. However,

one third (33%) of respondents considered a DNR order to be the impetus to consider or implement limitation of other life-sustaining therapies not related to cardiopulmonary arrest with 6% reporting that a DNR order indicates a transition to comfort care only. This interpretation is in striking contrast to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, which reads "Any DNR policy should ensure that the order not to resuscitate has no implications for any other treatment decisions. Patients with DNR orders on their charts may still be appropriate candidates for all other vigorous care." The disconnect between practitioner understanding and the actual intent of a DNR order can create confusion and discord between the healthcare team and the family. This confusion may prove particularly problematic as withholding cardiopulmonary resuscitation often represents a common ground from which consensus may be built in situations of grave prognosis and disparate opinions. Moreover, it is important to recognize that DNR orders should be periodically revisited particularly with changes in the child's condition or when the potential need for an interventional procedure arises.

The discussions regarding the withdrawal of life-sustaining therapies versus withholding or limiting those therapies can be confusing for both families and clinicians, resulting in ethical conflict and possible moral distress. The underlying premise of either discussion is that curing the critical or underlying illness is no longer possible or that it is so improbable that the risk of pain and suffering far outweighs the benefit of providing life-sustaining therapies. Both discussions signal a shift in patient care goals that may be difficult for families and, many times, for clinicians to accept. Targeted care conferences between the family and healthcare team are crucial to discuss options, answer questions, and optimally inform decisions. The goal is to form consensus such that all individuals involved agree with the decisions. The use of the communication approaches described above may be pivotal in achieving this goal.

The shift in patient care goals are based on a decision either to withdraw certain life-sustaining therapies or to limit the start of any new such therapies. Examples of common life-sustaining therapies that may be withdrawn or limited include the use of mechanical ventilation, vasoactive agents, antibiotics, blood products and hydration or nutrition. *Withdrawal* of life-sustaining therapies refers to the active removal of a therapy that has already been initiated, whereas the *withholding*, or *limiting*, of life-sustaining therapies means that new life-sustaining interventions will not be started. Both decisions are based on the general premise that the child is dying, and continuation of life-sustaining therapies or initiation of new such therapies will only serve to prolong or exacerbate suffering with little or no hope for meaningful recovery. In general, it is accepted that there is no ethical difference between a decision to withdraw or to withhold a potentially life-sustaining therapy. Moreover, it is important to recognize that once death is determined to be the expected outcome for the child, not removing or not starting therapies that would *artificially* prolong life is ethically justified. Additionally, it is important to note that the cause of death is the underlying life-threatening condition and not the withdrawal of support.

In general, it is accepted that there is no ethical difference between a decision to withdraw or to withhold a potentially life-sustaining therapy.

The delivery of compassionate EOL care is frequently focused on managing symptoms, especially pain, anxiety, and dyspnea. However, most medications used to relieve these symptoms, such as opioids and anxiolytics, have the potential for significant side effects, particularly respiratory depression and cardiovascular collapse. Given the risk of such side effects, clinicians are often worried that administration of these medications may actually hasten death. The goal of palliative care medicine including palliative sedation therapy is never to hasten death. This perceived ethical conflict related to the risks and benefits of administering anxiolytic, sedating, and opioid pain medications is addressed by the Doctrine of Double Effect which states that an action has two effects: one that is inherently good and one that is inherently bad, yet justifiable.

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Specifically, within the Doctrine, the following conditions must be met: (1) the nature of the act must be good or at least morally neutral; (2) the clinician's intention must be to only provide the good effect; (3) there must be a distinction between means and effect, such that the bad effect must not be a means to a good effect; and (4) there must a proportionality between the good effect and the bad effect (i.e., the benefits of the good effect must outweigh the risk of the bad effect). Simply stated, administering anxiolytic, sedating, and/or opioid pain medications to a child at the end of life with the sole intention of relieving pain and suffering is ethically and morally justifiable, despite the risk of causing respiratory depression, and/or hypotension, and the concern of hastening death.

Disagreements about the perceived effectiveness of a given therapy is often a source of conflict and distrust between families and the healthcare team. When these disagreements occur during EOL decision-making, the result may be ethically troubling for the PICU team caring for the child. Conflict often occurs when a family requests or demands initiation of a therapy that the clinicians believe to be either ineffective or inappropriate in relationship to the child's condition. Both the family and healthcare team believe they are acting in the child's best interest, but clinicians may feel pressured to initiate a therapy that they believe will not help the child and may even cause further distress for the child. Such conflict may be the source of moral and ethical distress for the healthcare team, as the primary goal of providing healthcare is based on the ethical principle of beneficence, or "do no harm." Consequently, clinicians have no obligation to provide truly "futile" therapies, which are defined as those therapies that are unable to meet physiologic goals, nor should they if they believe that such therapies will cause harm.

Recommendations for the management of requests from patients and families for treatment the healthcare team believes to be inappropriate and ineffective are addressed in a recent consensus policy statement from the Society of Critical Care Medicine, American Association of Critical Care Nurses, American Thoracic Society, American College of Chest Physicians, and the European Society for Intensive Care Medicine.

Recommendations for the management of requests from patients and families for treatment the healthcare team believes to be inappropriate and ineffective are addressed in a recent consensus policy statement from the Society of Critical Care Medicine, American Association of Critical Care Nurses, American Thoracic Society, American College of Chest Physicians, and the European Society for Intensive Care Medicine. These clinical recommendations include: (1) creating institutional strategies, such as proactive communication and expert consultants, to minimize or prevent care disputes; (2) using the term "potentially inappropriate" rather than "medically futile" or "futility" when discussing treatments that may have some chance of meeting a patient care goal, no matter how small, but that the clinicians believe are clinically not indicated and their non-use ethically justified; and (3) saving the term "futile" to use only in those specific occasions in which the family requests care that cannot achieve the intended goal in any way. Initiation of family meetings early in the PICU admission is fundamental to creating a trusting environment and effective communication between the family and healthcare team. Creating a strong foundation of trust is essential to establishing mutually agreeable EOL care goals for a child.

Solid organ transplantation in children is incredibly complex and fraught with challenges related to the availability of appropriately sized donor organs. Concurrently, the development and improvement of supportive technologies and interventions for children with primary organ failure are increasing the number of children awaiting transplantation, thus, increasing the demand for viable pediatric donor organs and creating ethical concerns for care providers. Living donor transplants of the liver and kidney may be suitable options for children

requiring transplantation, yet the majority of transplanted organs in children are procured from brain dead donors. In 1981, the Uniform Determination of Death Act (UDDA) established what is known as the "Dead Donor Rule," which states that "vital organs should only be taken from dead subjects and, correlatively, living subjects must not be killed by organ retrieval." As the UDDA did not adequately address the unique aspects and challenges of declaring brain death in infants and children, guidelines for the determination of brain death in children were published in 1987 and updated in 2011 (► Chap. 24).

As the demand for viable donor organs continues to grow, alternate procurement and transplantation methods have been developed and tested. One controversial method is organ donation after cardiac death (DCD), previously referred to as "non-heart-beating organ donation." Donation after cardiac death typically occurs after withdrawal of life-sustaining therapies when the donor has been declared dead by circulatory standards, i.e., by cessation of circulation. Although such transplant practices vary, the following conditions generally must be present prior to DCD donation: (1) informed written consent for DCD must be obtained from the parents or legal guardians; (2) there must be irreversible, end-stage illness where a decision to withdraw life-sustaining therapies was made *prior* to the decision to donate; (3) withdrawal of support must occur in the intensive care unit or operating room to assure adequate management of donor pain and anxiety; (4) a specified observation period must be provided (generally 60 to 120 minutes); and (5) if cardiac function and circulation stop within the observation period, the patient may be declared dead and the organs procured after a waiting period of approximately 2 to 5 minutes. If these conditions are not met during the observation period, the patient is no longer considered a potential DCD donor, and EOL care is continued.

Donation after cardiac death typically occurs after withdrawal of life-sustaining therapies when the donor has been declared dead by circulatory standards.

Organ donation by cardiac death, while supported by some professional organizations, remains controversial. It is not the standard of care, and it engenders ethical concerns. Some of the concerns include the issues that donors may experience pain and suffering if death is declared prematurely, that DCD violates the "Dead Donor Rule," that irreversible damage to the donated organs may occur from ischemia if death is not pronounced within the necessary time frame, and that a conflict of interest may exist between the needs of the donor and the needs of the transplant recipient.

49.5 Parental Bereavement Care After the Death of a Child in the PICU

49.5.1 Definitions

Bereavement is the term used to denote the objective situation of having lost a significant other to death. Bereavement is a natural human experience and although associated with intense suffering for some individuals, most people adjust to their loss over time. *Grief* is the term used to describe the emotional reaction to the loss of a loved one. Grief is a primarily negative emotional reaction that includes diverse psychological and physical manifestations. Symptoms vary from person to person, from one culture to another, and over time. Grief can sometimes become complicated, traumatic, or prolonged. When this happens, grief deviates from the cultural norm in terms of intensity, duration, or degree of functional impairment. *Mourning* is the term used to refer to the public display of grief. In other words, mourning refers to the social expressions that are often shaped by beliefs and practices of a given society or cultural group.

Bereavement is the term used to denote the objective situation of having lost a significant other to death. Grief is the term used to describe the emotional reaction to the loss of a loved one. Mourning is the term used to refer to the public display of grief.

49.5.2 Health Outcomes of Bereavement

The grief associated with the loss of a child has been suggested to be more severe than that associated with the loss of a spouse, parent, sibling, or other person.

The death of a child is a devastating experience for parents and families. The grief associated with the loss of a child has been suggested to be more severe than the grief associated with the loss of a spouse, parent, sibling, or other person. The intensity of parental grief after a child's death likely relates to the close and enduring nature of the parent-child relationship, the disruption in natural order that occurs when a child dies before the parent, feelings of parental guilt and failure to protect the child, and disruption in family structure.

Bereaved parents have been found to have increased rates of adverse mental health outcomes.

Complicated grief is a chronic debilitating condition characterized by persistent separation and traumatic distress that interrupts the grieving process.

Many studies have demonstrated increased morbidity and mortality among bereaved parents. Bereaved parents have been found to have increased rates of adverse mental health outcomes including depression, anxiety, post-traumatic stress, complicated grief, and first-time psychiatric hospitalizations. Complicated grief is a chronic debilitating condition characterized by persistent separation and traumatic distress that interrupts the grieving process. Core symptoms include yearning and sorrow, anger and bitterness, preoccupation with thoughts of the deceased, and difficulty accepting the reality of the death. Complicated grief causes clinically significant impairment in social, occupational, and/or other important areas of functioning. A diagnosis of complicated grief is typically not made until at least 6 months have elapsed since the death. Approximately 5–10% of bereaved people are believed to suffer from complicated grief. However, among parents whose children die in a PICU, 60% have symptoms consistent with complicated grief 6 months after the death, which persist in 40% at 18 months.

The effects of bereavement on physical health are more controversial. Some studies have found increased rates of cancer, diabetes, myocardial infarction, newly diagnosed chronic conditions, and medication changes, whereas other studies have not. In a recent study of parents' physical health after the death of an infant or child in the NICU or PICU, parents' acute illnesses, hospitalizations, and medication changes were greatest between 1–6 months and 11–13 months after the death suggesting parents' health be monitored and interventions targeted to parents during these intervals. Another recent study found parents' social health, reflecting the parent's perceived ability to participate in social activities, to be more severely impaired than their mental or physical health, or sleep during the first 6 months of bereavement.

Mortality rates for bereaved parents have been found to be higher than for non-bereaved parents. The risk of mortality is higher for bereaved mothers compared to fathers and higher when the child's death is due to unnatural causes (e.g., trauma, suicide, homicide).

Mortality rates for bereaved parents have been found to be higher than for non-bereaved parents. The risk of mortality is higher for bereaved mothers compared to fathers and higher when the child's death is due to unnatural causes (e.g., trauma, suicide, homicide). Physiologic changes underlying increased risk of morbidity and mortality during parental bereavement have been suggested to include neuroendocrine activation, altered sleep, immune imbalance, inflammatory cell mobilization, prothrombotic response, and hemodynamic changes, particularly early after the loss.

49.5.3 Risk and Resilience Factors Contributing to Parents' Health Outcomes

The Integrative Risk Factor Framework of Bereavement conceptualizes risk and resilience factors that influence parents' bereavement health outcomes.

The *Integrative Risk Factor Framework of Bereavement* conceptualizes risk and resilience factors that influence parents' bereavement health outcomes. Risk factors have an adverse impact on parental bereavement, whereas resilience factors promote healthy adjustment to loss. The integrative framework groups risk and resilience factors as (1) loss-oriented and restoration-oriented stressors, (2) intrapersonal factors, (3) interpersonal factors, and (4) coping and appraisal.

Loss-oriented stressors relate to some aspect of the loss experience itself (e.g., circumstances of the death), whereas restoration-oriented stressors are second-

ary stressors that relate to ongoing life (e.g., financial problems). Intrapersonal factors are stable factors intrinsic to the bereaved individual (e.g., personality). Some intrapersonal factors such as trait optimism (i.e., tendency for favorable expectations for the future), psychological flexibility (i.e., capacity to regulate behavior, emotions, and coping), and trait mindfulness (i.e., tendency for purposeful attendance to the present moment) can contribute to a bereaved individual's resilience. Other intrapersonal factors such as neuroticism (i.e., tendency to respond to loss with negative emotion) or preexisting substance abuse or mental illness may contribute to increased risk of adverse outcomes.

Interpersonal factors are factors external to the individual (e.g., family support). For example, good communication between spouses may help to minimize spousal differences in grieving. This may be important as differences in grieving between spouses can be a risk factor for poor outcome. Additionally, perceived social support and in some cases religious practices and spirituality increase resilience during bereavement. Greater use of spiritual activities among bereaved parents has been associated with lower symptoms of grief and depression, as well as lower symptoms of post-traumatic stress in mothers. Additionally, mothers with more frequent use of religious activities (e.g., attending church, praying, trusting in God) exhibited greater personal growth.

Coping is the process by which a bereaved individual appraises the personal significance of the death and their options for dealing with the loss. Coping likely mediates the relationship between risk and resilience factors and bereavement outcomes. The *Dual Process Model of Coping with Bereavement* holds that bereaved individuals need to oscillate between coping with loss-oriented stressors and restoration-oriented stressors to achieve healthy adjustment. Complications in grieving may occur when an individual's coping process focuses exclusively on loss or exclusively on restoration. Either reaction without any oscillation is extreme and may put a person at risk for adverse health outcomes.

The Dual Process Model of Coping with Bereavement holds that bereaved individuals need to oscillate between coping with loss-oriented stressors and restoration-oriented stressors to achieve healthy adjustment.

Meaning making is a coping strategy that attempts to restore meaning following a highly stressful situation. The extent to which parents make sense and find meaning in their child's death may be inversely related to their degree of distress and directly related to their sense of personal growth during bereavement. *Rumination* is a coping style consisting of recurrent, self-focused, negative thinking. Although a normal part of grief, extreme rumination may lead to poor bereavement outcomes. A greater understanding of the risk and resilience factors as well as the coping mechanisms used during bereavement may allow for the development of screening tools for parents at risk for adverse outcomes, and potentially, interventions to promote resilience in high-risk parents.

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49.5.4 The Role of the Critical Care Provider in Family Bereavement

49.5.4.1 What Can Critical Care Health Professionals Do to Help Parents Through the Bereavement Process?

Relationships between parents and healthcare professionals in the PICU develop and change during the course of a child's critical illness and death. The *Theory of Transitional Togetherness* describes the core processes of these relationships that are proposed to exist in three phases reflecting the changing needs and priorities of parents during their PICU stay and subsequent bereavement. The first phase, *Welcoming Expertise*, describes the initial formation of the parent-health professional relationship. It focuses on the parent recognizing the expertise of healthcare professionals and relinquishing care of the child to these providers to enable the child's recovery. The second phase, *Becoming a*

The Theory of Transitional Togetherness describes the development and change in the relationship between parents and healthcare providers during the course of a child's critical illness and death. It consists of three phases: (1) Welcoming Expertise, (2) Becoming a Team, and (3) Gradually Disengaging.

Team, begins as the parent realizes that recovery is not possible and the child will likely die. During this phase, parents attempt to reconstruct a role for themselves in the ICU and desire to work with healthcare professionals to care for their child. The third phase, *Gradually Disengaging*, describes parents' desire for their relationship with healthcare professionals to continue after the child's death until no longer needed. Gradually disengaging includes the themes *Saying Goodbye*, *Going Home*, and *Ongoing Support*.

At the time of the child's death, healthcare providers can guide parents through the process of saying goodbye to their child. Supportive actions often include legacy making, providing private space, and allowing sufficient time with the child's body so that the parents do not feel rushed. Legacy making consists of actions or behaviors aimed at remembrance. Examples include ink handprints and footprints, plaster impressions, locks of hair, photographs, digital storytelling, memory boxes, and other personal keepsake items. 3D printing is now being utilized to create hand and foot molds for remembrance. Good memories created with parents during this time are long-lasting and can bring comfort to parents not only in the present moment, but also later in bereavement.

After saying goodbye to the child, healthcare professionals can support parents during the process of leaving the hospital and going home. Walking parents out of the hospital, making sure they are not alone, and providing the healthcare professional's contact information are examples of ways to support parents during this phase.

Many parents describe a need for longer-term ongoing support from their child's healthcare professionals with whom they already have an established relationship. However, it is important to realize that not all parents desire this type of ongoing support. Most parents appreciate acts of kindness and commemoration from the staff such as sympathy cards, letters, telephone calls, and attendance at funerals and memorials. Parents who desire an ongoing relationship with staff often feel abandoned if further contact is not offered. Usually, parents want more contact from staff early after the death with support gradually tapering off over the first year. A follow-up meeting between parents and healthcare professionals in the weeks to months after a child's death is one way to provide parents with additional information, emotional support, and an opportunity to provide feedback regarding their experiences.

49.5.5 Bereavement Interventions

Although the loss of a child can put parents at risk for adverse health outcomes, there is no evidence to suggest that all bereaved parents need or will benefit from intervention. In a recent review of interventions for bereaved parents following a child's death, four types of interventions were identified including support groups, counseling, psychotherapy, and crisis intervention. The review found very limited evidence to demonstrate efficacy of any of these intervention techniques to assist parents after a child's death.

Grief interventions have been described as primary, secondary, and tertiary preventive interventions. Primary interventions consist of professional support that is available to all bereaved individuals. Primary interventions may be helpful if left to the initiative of the bereaved individual. Secondary interventions are intended for individuals found to be at high risk for bereavement-related health problems through screening or assessment. Tertiary interventions are those that provide therapy for bereavement-related health problems such as complicated grief, depression, or post-traumatic stress disorder.

Complicated Grief Therapy (CGT) has become the treatment of choice for adults with complicated grief. This therapeutic intervention consists of 16 sessions that are conducted in a staged process. The effects of this targeted therapy were recently confirmed in a placebo-controlled, randomized clinical trial evaluating the efficacy of CGT among adults meeting diagnostic criteria for complicated grief. In this study of 395 bereaved adults, participants' response to CGT compared to no therapy was 82.5% vs. 54.8%, respectively (RR 1.51; 95% CI, 1.16–1.95; $P = 0.002$; NNT 3.6), suggesting efficacy of CGT for treating adults with complicated grief. Of note, 20% of the total study population consisted of bereaved parents, and 48% of this group received CGT.

Complicated Grief Therapy (CGT) has become the treatment of choice for adults with complicated grief with its efficacy being confirmed in a placebo-controlled, randomized clinical trial.

In comparison to CGT, pharmacologic treatments for complicated grief have demonstrated underwhelming effects. Early studies examining the effects of tricyclic antidepressants, as well as bupropion, resulted in small sample sizes and demonstrated at most moderate improvement in grief intensity or symptoms, with a larger impact seen on symptoms of depression. More recent investigations on the use of selective serotonin reuptake inhibitors (SSRIs) for complicated grief have been slightly more promising. However, the addition of citalopram to participants receiving CGT in the above trial did not improve their complicated grief response rate when compared to placebo. Depressive symptoms were again, however, significantly decreased in this population. At this time, it appears that no class of antidepressant is solely effective in treating bereaved individuals with complicated grief, but SSRIs in conjunction with CGT may offer relief for individuals with co-existing symptoms of depression.

At this time, it appears that no class of antidepressant is solely effective in treating bereaved individuals with complicated grief, but selective serotonin reuptake inhibitors (SSRIs) in conjunction with CGT may offer relief for individuals with co-existing symptoms of depression.

The death of a child is a devastating experience for parents and families. Many bereaved parents suffer adverse mental and physical health consequences after their child's death. High-quality relationships and open communication between parents and healthcare professionals are foundational to effective bereavement support in the PICU. Although there is no evidence to suggest that all bereaved parents need intervention, parents experiencing complicated grief may benefit by referral to a mental health professional.

Many bereaved parents suffer adverse mental and physical health consequences after their child's death. High-quality relationships and open communication between parents and healthcare professionals are foundational to effective bereavement support in the PICU. Although there is no evidence to suggest that all bereaved parents need intervention, parents experiencing complicated grief may benefit by referral to a mental health professional.

49.5.6 Bereavement Support Considerations for Siblings

Bereavement support for siblings is another important consideration when a child dies in the PICU. Support for bereaved siblings requires a developmental understanding of end of life and grief. For infants and toddlers (less than 2 years), attachment is a central developmental theme. Fostering opportunities for secure attachment such as ensuring a safe and nurturing environment, use of transitional objects, and support for parents so they can care for their young children are important considerations.

Support for bereaved siblings requires an understanding of end of life and grief based on their developmental stage.

During early childhood (2–6 years), children are usually in the preoperational stage of development. Bereaved siblings of this age may engage in regressive behaviors that remind them of a more secure developmental period. Play therapy may serve as a way for children of this age to communicate and work through their experience as a bereaved sibling.

School-age children (7–12 years) are typically within the concrete operational stage. Bereaved siblings of this age may ask more direct questions and benefit from open discussion about death. School-age children may also benefit from support groups or camps that allow connection with other bereaved children.

Adolescents and young adults are within the formal operational stage where abstract thinking and integration of personal identity are central devel-

opmental themes. Grief may lead to a sense of loss of self and participation in high-risk behaviors. Support may involve helping teens find personal meaning, make social connections, and participate in legacy building. Camps and online communities may be beneficial, as well as time alone or with peers.

49.6 Summary

Although the recognition of palliative care medicine as a subspecialty in 2006 has spearheaded significant advancements in the field and spawned an ever-growing body of specially trained clinicians, it is important to remember that the provision of quality palliative care is the responsibility of all participating in the care of children diagnosed with a potentially life-limiting condition and their families. Quality end-of-life care is an essential component of any multidisciplinary pediatric critical care program. The identification and successful treatment of the physical, psychosocial, spiritual, and environmental needs of the child and his/her family at the end of life may minimize suffering and provide much comfort.

However, the provision of quality end-of-life care presents many challenges to the multidisciplinary healthcare team. Comprehensive and time-intensive care may be particularly challenging for the critical care provider who is confronted with simultaneously caring for other critically ill children. Additionally, the pediatric critical care provider must be familiar with the many potential ethical issues associated with end of life including the appropriate use of "Do-Not-Resuscitate" orders, the difference between withdrawal and limiting of life-sustaining therapies, the Doctrine of Double Effect, recognizing conflict associated with potentially futile or inappropriate therapies, and navigating the challenges of organ donation after cardiac death. Finally, the pediatric intensive care clinician must understand the concepts of bereavement, grief, and coping and recognize the actions that might help families work through the most difficult of losses, the death of their child. Although challenging, the provision of quality end-of-life care with clear, compassionate communication and effective treatment of distressing symptoms holds the potential to provide an everlasting source of comfort to the child and family in most need.

Chapter Questions

1. The dead donor rule was established by what legal document?
   (a) The Belmont Report
   (b) The Common Rule
   (c) The National Research Act
   (d) The Uniform Determination of Death Act

2. Which statement is **true** regarding the determination of pediatric cardiopulmonary death following the withdrawal of support?
   (a) A pediatric patient has had no pulse and is apneic after 2 minutes, but pulseless electrical activity (PEA) is seen on the cardiac monitor; therefore they do not meet criteria for cardiopulmonary death.
   (b) A pediatric patient has had no pulse and is apneic after 5 minutes, but pulseless electrical activity (PEA) is seen on the cardiac monitor. They do not meet criteria for cardiopulmonary death.
   (c) Autoresuscitation has played no role in the establishing the criteria for the determination of cardiopulmonary death.
   (d) A pediatric patient has had no pulse and is apneic after five minutes, but pulseless electrical activity (PEA) is seen on the cardiac monitor. They do meet criteria for cardiopulmonary death.

3. A 9-year-old female has had support withdrawn. She has had no pulse and has been apneic for 5 minutes, but pulseless electrical activity (PEA) persists on the cardiac monitor. Does she satisfy the criteria for cardiopulmonary death?
   (a) No, asystole needs to be observed on the monitor.
   (b) No, the potential for autoresuscitation is high and must be excluded.
   (c) No, unless the parents have consented for organ donation after cardiac death.
   (d) Yes, electric cardiac monitoring is not part of the criteria for determining cardiopulmonary death.

4. Which medication that is used in palliative sedation has been found to reduce neuropathic pain in children at the end of life?
   (a) Dexmedetomidine
   (b) Fentanyl
   (c) Ketamine
   (d) Propofol

5. Which statement best highlights the components of high-quality communication that is necessary at the end of a child's life?
   (a) "Mr. and Mrs. Smith, the unit is busy, but I wanted to take a quick moment to update you? I just finished looking at your son's scans. His mass may be a bit bigger, but I'm unsure. I would prefer your oncologist talk to you about this. Dr. Blue will be up shortly to discuss next steps. In the meantime, I'll keep handling the ICU issues. He is doing fine."
   (b) "Mr. and Mrs. Smith, is this a good time for you to sit down and talk? I know these past few days have been rough and likely very draining. Do you think Sam is having pain, or does he seem comfortable to you? I just finished reviewing Sam's scans with the radiologist and your oncologist, Dr. Blue. We agree that Sam's mass looks bigger and doesn't seem to be responding to his current treatment. We all wanted better news today, but clearly no one wanted it more than the two of you. Dr. Blue will be up shortly to discuss next steps, but I want you to be prepared for the fact that there may not be any other treatment options for Sam. I don't say that to take away your hope, but rather to be completely honest with you about what I am thinking."
   (c) "Mr. and Mrs. Smith, is this a good time for you to sit down and talk? I hate to have to share bad news, but it looks like your son's malignancy is larger and he doesn't seem to be responding to his current chemotherapeutic regimen. Dr. Blue will be up shortly to discuss next steps. He and I still need to discuss treatment options, but I want you to be prepared for the fact that there may not be any other treatment options for your son."
   (d) "Mr. and Mrs. Smith, the unit is busy, but I wanted to take a quick moment to update you. In brief, Sam's cancer is back. We don't think there are any more treatment options, but Dr. Blue will be up shortly to discuss next steps. I don't say that to take away your hope, but things don't look good."

6. Which of the following is the most established therapy for complicated grief in adults?
   (a) Amitriptyline
   (b) Bupropion
   (c) Citalopram
   (d) Complicated Grief Therapy

7. Bereaved siblings of which of the following age group are most likely to engage in regressive behaviors that remind them of a more secure developmental period?
   (a) Infants and toddlers less than 2 years of age
   (b) Children between 2 and 6 years of age
   (c) School-age children between 7 and 12 years of age
   (d) Adolescents over 12 years of age

Answers

1. D
2. D
3. D
4. C
5. B
6. D
7. B

Suggested Readings

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Outcome-Based Clinical Decision-Making in Pediatric Critical Illness

Steven E. Lucking

Contents

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Learning Objectives

- Explain why injury prevention is important in pediatric critical care medicine.
- Explain how process measures are not outcomes but may contribute to optimal outcomes.
- State the definition of "quality" and "value."
- List and describe several functional outcomes.
- Describe the history and utility of the available outcome measures for pediatric critical illness.
- Describe how to query data sets to assess performance of PICU units.
- Explain the value of being inquisitive at the bedside (i.e., reflective learning) to identify opportunities to improve outcome.
- Discuss our responsibility to advocate for the most appropriate quality and outcome tools.
- Describe why we should advocate for transparency and information sharing to develop best practices.

50.1 Introduction

Fundamental physiologic approaches to the care of the critically ill and unstable child with life-threatening single or multiple organ failure appear to vary dramatically throughout the United States.

The chapters of this textbook are designed to guide young critical care physicians toward a mastery of the fundamental principles of our specialty, both for the purpose of achieving certification and for the purpose of guiding the treatment of those children entrusted to our care. Charged with caring for the most seriously ill and injured children, how do we know if we are doing well and if we could do better? As in other specialties, the fundamental physiologic approaches to the care of the critically ill and unstable child with life-threatening single or multiple organ failure appear to vary dramatically throughout the United States, let alone throughout the developed world. For example, is it optimal that there is a five- to tenfold variation in the frequency of using nitric oxide (NO) for hypoxemic respiratory failure? Why is there at least a two- to fourfold difference among institutions that provide extracorporeal support in-house for severe ARDS? Should there be significant differences between institutions with similar levels of patient acuity for the use of continuous renal replacement therapies (CRRT), knowing that studies of CRRT failed to demonstrate any intrinsic benefit.

Almost all pediatric diseases, especially those requiring PICU care, can be classified as rare using the NIH definition of a prevalence of less than 200,000 affected individuals in the United States. Therefore, few individual PICUs care for a sufficient number of children to perform randomized controlled trials (RCTs). This mandates the use of collaborative improvement networks that facilitate practice-based teams learning from one another to test changes to improve quality and use their collective experience and data to understand and ultimately implement and spread interventions that improve care. Clearly successful examples of this approach include the Children's Oncology Group and more recently collaboratives like Improve Care Now for inflammatory bowel disease and the Cystic Fibrosis Foundation Care Network. For example, optimized care protocols were developed and implemented in pediatric oncology, focusing on preferred chemotherapy agents and doses within well-defined disease scenarios, utilizing cancer markers and staging, which resulted in steady improvement in the outcome of children with cancer.

There is a fundamental difference between improving the symptoms of organ dysfunction and optimization of organ function.

To improve care in the PICU, we need to identify the best pharmacologic support, mechanical support, and team performance characteristics. In addition, our patients commonly have multi-organ involvement, defying simple

protocolization. For example, what appears to be single-organ respiratory failure requires management of cardiopulmonary interactions to optimize pulmonary function while also considering the need for sedative agents with their own cardiovascular adverse effects. Indeed, mechanical ventilation and other mechanical respiratory supports do not directly improve pulmonary function; instead, these modalities support gas exchange in the presence of pulmonary dysfunction. Pulmonary function is optimized by addressing all of the lung interactions considering the inflammatory cascade, hydration status, cardiac output and its effect on dead space, central venous oxygen saturation (SvO_2), etc. I would argue that as long as high plateau pressure and high inspiratory flow rates are avoided, the choice of ventilator settings and modes of ventilation is one of the least significant determinants of outcome for most patients with respiratory failure since there is a fundamental difference between improving the symptoms of organ dysfunction and optimization of organ function.

Our specialty has made significant strides in developing multicenter collaborative research, including prospective clinical trials. The Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network (► https://www.palisi.org/) started over 20 years ago and since 2002 has published results of network studies and clinical trials. These studies include prospective multicenter randomized clinical trials of activated protein C in sepsis, prone positioning, exogenous surfactant in severe acute lung injury, hypothermia for in-hospital and out-of-hospital cardiac arrest, tight glucose control, packed red blood cell transfusion thresholds, etc. While some studies provided definitive answers to questions, the results from a few studies were either arguably equivocal, due to sample size, or uninterpretable due to protocol violations.

With the logistical and cost limitations for conducting multicenter randomized controlled trials, there are two main avenues of learning and clinical practice development for pediatric critical care practitioners. The most obvious of these is extrapolation from adult critical care studies. Historically, the results of adult randomized studies had to be carefully weighed regarding their potential applicability to our patients. For instance, the ARDS Network (► http://www.ardsnet.org/) study had limitations with reference to the seemingly non-standard of care treatment of the control patients and the fact that non-eligible patients, who probably received the current standard of care, did as well as the study group. The results of this trial were shown to not be applicable to children where small ventilator tidal volumes never have been demonstrated to be superior. However, other adult study areas, such as nutrition in critical illness, might offer insights that can be adapted to the pediatric population. Similarly, strategies that assist recovery of function after adult brain injury may be applicable to the care of younger humans. Whether pediatric intensivists feel comfortable applying the insights from adult critical care nutrition studies or not, they should certainly be knowledgeable of the results of those studies.

Reflective learning includes the steps of association, integration, validation, and appropriation.

The second method of practice development is called *reflective learning*. The study of reflective learning in health professions began in the 1980s and continues to be regarded as an important way that health professionals continue lifelong learning. Through attention and questioning, one develops hypotheses, tests them, and develops beliefs that drive learning and practice. One model of reflective learning describes the steps of association, integration, validation, and appropriation. The professional who successfully practiced reflective learning is described as self-aware and able to engage in self-monitoring and self-regulation. Unfortunately, the evidence to support methods of teaching reflective learning and to evaluate the outcomes of reflective learning remain elusive. In the absence of randomized clinical trials to guide pediatric critical care decision-making, most experienced pediatric critical care

practitioners have constructed a large proportion of their practice preferences through reflective learning, standards as yet unproven by experimental evidence. This approach likely explains, at least in part, the wide variation of practice observed in the PICU for specific conditions.

50.2 Defining Quality and Outcomes

The Institute of Medicine (IOM) defined quality as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." They identified six characteristics of quality, whereby care should be:

- *Safe* – avoiding injury/harm from the care provided, such as medication errors, mislabeled specimens, diagnostic errors, delayed or wrong therapy, unplanned extubation, etc.
- *Timely* – delivering care in a timely manner and avoiding potentially harmful delays. This includes early recognition and treatment along with improving patient flow such as resulting in timely transfer from the ED/OR to the PICU as well as appropriate transfer from the PICU to assure there is a bed available for the next new patient.
- *Efficient* – avoiding waste and providing care that is evidence-based and known to reduce waste and provide value, such as avoiding unnecessary transfusions or NO use. Efficient care also includes avoiding overprocessing and duplicating laboratory or other diagnostic studies. Other examples include early discontinuation from mechanical ventilation, which may be facilitated by 24/7 ICU attending coverage.
- *Effective* – using evidence-based practices that were shown to be effective. Effective care also means avoiding the use of ineffective care (i.e., effective care limits *overuse*, *underuse*, and *misuse* of interventions). Examples of effective care include implementation of care bundles to reduce the risk of central line and urinary catheter-associated infections and surgical site infections.
- *Equitable* – avoiding differences in provision of care based on race, age, gender, socioeconomic status, or medical condition (e.g., HIV).
- *Patient–/family-centered* – providing care based on the patient's preferences, needs, and values and ensuring that all clinical decisions are guided by the patient's values. This means sometimes focusing on end-of-life care and managing pain rather than cure.

An often-referenced approach to quality assessment was proposed by Donabedian more than 30 years ago. Although this methodology was useful at that time, current electronic medical record (EMR) systems and computerized hospital databases permit better measurement of *outcomes that matter to patients*. Unfortunately, the Donabedian elements are still collected and used to assess quality by various organizations, so it is important to understand the terms and their limitations as quality measures.

Structure involves factors that can influence or enable processes, such as the type of facility, staffing numbers, and presence of equipment. The Agency for Healthcare Research and Quality (AHRQ) defines structure as the features of organizations or clinicians that are relevant to their capacity to provide healthcare. Thus, structural measures are one step removed from process measures and two steps removed from outcomes. Examples of structural measures are listed in ◘ Table 50.1. Note that none of these structural measures assure optimal patient outcome; the relationship between structure and outcome is weak at best.

Table 50.1 Donabedian approach to measuring quality

Structure	Process	Outcomes
Number of ICU beds	VAP, CLABSI, CAUTI, pressure ulcer, and unplanned extubation care bundle compliance	Mortality (risk adjusted)
Nurse to patient ratio	Use of order sets – e.g., bronchiolitis, ventilator weaning	Rate of VAP, CLABSI, CAUTI, pressure ulcers, unplanned extubations
Equipment and supplies available, e.g., ultrasound for CVL placement, which does not assure it is used or used correctly	Time to first antibiotics	Length of stay (PICU, hospital) (ideally risk adjusted)
Training, e.g., the proportion of nurses who are PALS certified or who are trained in CAUTI prevention	Early goal-directed therapy bundle for sepsis compliance	New organ system dysfunction; functional outcome
24-h critical care attending coverage	Line insertion bundle checklist compliance	Cost of care (*not* charges)
Patient demographics	Compliance with use of safe surgical checklist in the OR	Patient/family satisfaction with outcome (*not* satisfaction with customer service)
Staffing – presence of respiratory therapist, PICU-assigned pharmacist	Scrub the hub compliance	Resolution of shock
Teaching hospital, children's hospital	Compliance with barcode medication administration	Diagnostic errors (missed, delayed, or wrong)
Availability of barcode medication administration	Recording standardized measures such as GCS in trauma patients or obtaining recommended labs and imaging studies for trauma, sepsis, etc	ICU/hospital readmissions
Availability of EMR		Disease-specific patient outcomes, such as hospital-acquired sepsis or hypoglycemia events during DKA treatment

CAUTI catheter-associated urinary tract infection, *CLABSI* central line-associated blood stream infection, *CVL* central venous line, *DKA* diabetic ketoacidosis, *EMR* electronic medical record, *GCS* Glasgow Coma Score, *PALS* Pediatric Advanced Life Support, *VAP* ventilator-associated pneumonia

The next element in the Donabedian approach to quality measurement is *processes* of care or the services and/or interventions delivered. Processes are different from outcomes; they may be correlated with outcomes but are one step removed from patient outcome (Table 50.1). Processes are often monitored

as a surrogate for outcome measurement because they are usually easier to collect and record compared with outcomes that matter to patients.

The final element in the Donabedian quality measurement approach is *outcomes* themselves, which are the actual results of care. As noted previously, there is not just one outcome, although mortality and length of stay are often used as the main outcome measures in the PICU.

Besides the Donabedian approach, other organizations use different definitions for quality and outcome measurement. Although the IOM report helped increase recognition of the importance of safety and quality, the definition for quality used by the IOM adds to the confusion. Quality outcome measures are often required by payers or regulatory agencies. For example, quality measures included in the National Quality Measures Clearinghouse are overwhelmingly process measures. Many third-party organizations developed "quality" measures, but the vast majority of these measures do *not* measure patient outcomes and instead measure process compliance or include patient satisfaction surveys that assess the patient/family's service experience. Of the 78 Healthcare Effectiveness Data and Information Set (HEDIS) measures, which is the most widely used quality measurement system, all but 5 are clearly process measures. Of these five, one is a health indicator, three are patient surveys of their care experience, and only one could be described as an outcome measure. The lack of clarity and use of "quality" and "outcome" that have different meanings creates confusion and obscures efforts to measure quality and increase value.

"Quality" refers to patient outcomes; however, the word has assumed various meanings and is widely misused.

Although outcome measures, such as the PICU rate of CLABSI infections, are often attributed to the care provided by the PICU team, the outcome for a child in the PICU often depends on the care provided by a team, which includes not only the providers assigned to the PICU but also specialists from other specialties and ancillary services such as radiology and pharmacy. For example, the PICU nursing and medical staff may provide optimal central line care, but if the patient goes to the OR and the anesthesiologist leaves the central line port open and does not clean the injection site between medication injections, the patient may develop a central line infection that is attributed to the PICU but actually resulted from care delivered outside the PICU.

The most important purpose of outcome measurement is improvement of care, not keeping score.

Sometimes the outcome attributed to the PICU may result from care defects outside of the PICU.

50.3 Understanding Value

Value refers to the output achieved relative to the cost incurred. In healthcare, value is defined as the patient health *outcomes* achieved per dollar spent. Defining and measuring value is essential to understand the performance of any organization and to drive continuous improvement. Ultimately, value is what matters most to patients and should unite all members of the healthcare system. Value encompasses many of the other goals embraced by healthcare, such as quality, safety, patient centeredness, and cost containment. Value is what matters to the *patient* rather than value for the providers or hospital. Although value should be the shared focus of the healthcare system, it is often unmeasured. *Profitability*, which is used in many industries as a proxy for value, is not a reliable metric of value in healthcare because of our currently flawed reimbursement system.

Value should be measured by outputs, not inputs. Thus, value depends on the actual patient health outcomes, not the volume of services delivered or the compliance with processes (bundles) of care. These measures may be related to outcomes, but they are not direct measurements of the outcome important to patients. Note that achieving high value is not a code word for "cost containment," although some providers may feel that way. Simply cutting costs may worsen patient outcomes. Cost cutting may be good for the health system's

bottom line, but not the quality of life for the patient and their family. Studies have shown, however, that achieving better outcomes not surprisingly reduces ICU length of stay and resource utilization; thus, this is usually associated with lower costs (i.e., these units achieve high value).

It is important to know that for any medical condition or patient population, there is often no single outcome that captures the results of care. Certainly, survival is important in the PICU, but if the patient is left with significant morbidity and impaired function, this is likely an unsatisfactory outcome for the patient and family and leaves them with significant care demands and costs. Recent data shows that development of a new morbidity is more than twice as likely than mortality following a PICU admission. Thus, limiting outcome assessment to just PICU mortality and length of stay misses outcomes that are important to patients and their families. Patient outcome is often revealed over time and manifested in longer-term outcomes such as sustainable recovery and return to normal activities of daily living versus the need for ongoing interventions and support or the occurrence of treatment-related illnesses, such as chronic renal failure or the need for respiratory support.

The denominator of the value equation is *cost*, which ideally should include the *total cost of care* involved in the full cycle of patient treatment rather than just the cost of PICU care or hospital care. The total cost of care includes the costs of subsequent hospitalization, possible rehabilitation, as well as follow-up outpatient care and ancillary services and equipment. Unfortunately, this detailed cost data is rarely captured.

One of the major issues with determining cost is determining how to allocate costs. Many of the costs in healthcare delivery are shared costs, involving shared resources such as imaging equipment, specialty physicians, support staff, facilities, equipment, and overhead expenses used to care for multiple patients. Even costs directly attributable to a patient, such as drugs, have expenses in addition to the drug acquisition cost, such as costs related to pharmacist review of the order and medication preparation. Currently, these costs are often calculated as an average cost determined from the care of all patients, which is then used to determine an hourly rate, such as used in the operating room. The challenge for clinicians wanting to understand value is to identify the actual costs assigned to an individual patient rather than the average cost. That is, the shared costs have to be allocated to individual patients based on the patient's proportional use of the shared resources.

Another cost that is difficult to quantify are the costs borne by patients and their families in supplementing their care after the PICU stay. Although survival following an ICU stay is important, we can't measure value without knowing the functional outcome of the child and the financial burdens families have to manage following hospitalization. Even costs such as lost work time by parents to care for their child should be part of the cost calculation when considering value.

Value is defined as the patient health outcomes achieved per dollar spent.

Even when costs are recorded in shared databases and analyzed for quality improvement purposes, these "costs" often represent some fraction of *charges* rather than true costs. The Healthcare Cost and Utilization Project (HCUP) Kids' Inpatient Database (KID) is often used in studies analyzing the costs of care. Hospitals submit their charges and provide an average cost/charge factor representing the mean of all costs and charges, which is then used by investigators to estimate costs; obviously, this is a crude method to determine actual costs.

Ideally, the total cost of care should be measured to determine value, but this parameter is uncommonly measured.

Finally, the use of claims data to estimate outcomes and costs by diagnosis or to identify diagnosis-related complications and conditions that occur during the hospitalization is limited by the accuracy and completeness of the coding used to describe the patient's condition. Studies have shown that coding often

Hospital costs typically are estimated by the product of patient charges and an overall hospital-specific cost/charge factor.

is assigned based on methodologies that maximize reimbursement rather than accurately identifying the patient's underlying conditions and any complications that occurred during the hospitalization.

50.4 Error and Adverse Event Prevention in the Intensive Care Unit

Starting with the recognition of the magnitude of the effect of medical errors on patient outcomes, highlighted in the 1999 publication, *To Err Is Human: Building a Safer Health System*, by the Institute of Medicine (IOM), there has been considerable focus on error prevention and patient safety to improve patient outcome. To that end, several error prevention strategies were demonstrated to be effective in the critical care setting.

For example, rounding checklists were shown to reduce errors of omission as well as reduce utilization of potentially harmful instrumentation such as urinary catheterization. However, this and other checklists were perceived as not helpful and viewed as over-standardizing care when borrowed from other settings and not adequately adapted to an individual ICU's needs. The articulation and recording of daily goals for each patient during rounds was not only associated with improved nursing and parent perception of communication but also a reduced ICU length of stay. It is hard to argue against better communication and having a shared understanding of the daily goals for each patient, whether they are stated as achievements for the day (e.g., initiation of breathing trials, extubation, initiation of feeding, awakening from sedation, etc.) or articulation of targets for goal-directed therapy specific to disease processes (e.g., targets for blood pressure, SvO_2, pH and $PaCO_2$, serum sodium, etc.). Both brevity and relevance to the particular ICU setting, along with consistency of use, are related to the effective use of rounding checklists. As we learn more about optimized care for various disease processes, it is likely that communication of our evidence-based targeted therapies will be increasingly beneficial.

The potential value of implementing a process measure (checklist compliance) was demonstrated by the World Health Organization's Safe Surgery Saves Lives program, which was rolled out to eight hospitals in eight cities in eight countries encompassing very diverse socioeconomic environments. This study observed significant reductions of complication and mortality rates. To the contrary, implementing surgical safety checklists on a large scale in Ontario, Canada, through the Ministry of Health and Long-Term Care failed to demonstrate any reduction in complication or mortality rates. Similarly, a regionally implemented pediatric surgical safety checklist was observed to have no effect on reducing complication rates.

This leads to the common perception that interventions that work in initial studies lose their effectiveness as they are implemented more widely. An alternative explanation is that what may work in a large, well-resourced system may not be practical or work well in less well-resourced settings. Furthermore, published outcome studies likely change behavior. For example, the well-accepted goal-directed therapy for sepsis appeared to lose its ability to improve outcome when compared with "usual care" in a recent large multicenter adult trial. It is important to recognize, however, that "usual care" in the control arm of this study now incorporated many of the elements of the original goal-directed care bundle.

In pediatrics, cardiac ICUs (CICU) were associated with improved outcomes when first established. As these CICUs became more widespread, studies reported that providing postoperative care in a CICU was no longer associated with improved outcome. The failure of this structural measure (i.e., CICU vs. PICU) to be associated with outcome illustrates that simply desig-

nating a unit as a CICU does not assure it is staffed with experienced providers to achieve improved outcomes.

Similar results regarding the loss of an intervention's effectiveness over time was observed with the implementation of rapid response teams (RRT). Initial studies suggested improved outcomes, but it is likely that the team composition and team member experience and training are not replicated across all pediatric centers that implemented an RRT. In addition, measuring the success of an RRT based on reducing patient mortality rate or achieving less frequent cardiac arrests is difficult since these are insensitive markers of intervention success since they are infrequent, especially in settings with lower patient acuity and complexity.

Rather than assuming that a process improvement intervention is flawed, some of these interventions could be adapted to improve outcome. When considering the adoption of a performance improvement (PI) intervention, the unit should identify the core concept(s) of what the PI activity is designed to achieve rather than the detailed tasks that are part of the intervention. Then, individual units can determine if the core concepts can be implemented in their setting using a different methodology or approach than that used in the well-resourced initial center study. For example, rather than requiring that an RRT should be activated based on a specific Pediatric Early Warning Score (PEWS), which may not be collected and automated at your institution, a core concept of an RRT is to use a reliable, reproducible method to identify deteriorating patients in real time. This may mean that you need to create a culture that enables a nurse or parent to activate an RRT based on their gut feeling that something is wrong so that timely assessment and intervention occurs. In addition, the team composition may vary depending on the resources available in that health system. Organizations should implement PI processes that work best in their system to achieve the core concept(s) of the intervention.

Finally, the evidence suggests that safety checklists and similar safety process bundles are potentially effective for error and complication prevention, but their effectiveness depends on the thoughtfulness of their development and how they are modified, embraced, and applied at the local institution. Mandated implementation on a large scale appears to be less effective than implementation with personal commitment at the institution level.

Safety checklists and other process interventions appear to lose their effectiveness when broadly implemented, but this may result from the need to modify the checklist to meet the needs and resources of the local institution.

Safety checklists have the potential to be effective for error and complication prevention, but their effectiveness is dependent on the processes used in their development and application.

PI tools are more effective when there is a commitment to improvement. PI tools are like flashlights; what seems to matter most is not so much dependent on the quality of the flashlight but rather the commitment of the person using the flashlight against the darkness. Conversely, a lack of engagement by leadership in the day to day, and hour to hour, functioning of the intensive care unit, resulting in lost understanding of the actual care processes, can have tragic consequences. Examples from our own specialty include the delayed recognition of the malevolent behavior of a pediatric ICU nurse in causing multiple unexpected deaths of children in a PICU in the 1980s. Another noteworthy example is the seemingly unanticipated increase in mortality at a prominent PICU at the time of computerized order entry implementation, whereupon further examination demonstrated that the new process resulted in a predictable and avoidable interference in the timeliness of care. Most recently, two academic children's hospitals are suffering because of their apparent unwillingness to appropriately respond to quality issues in their cardiac surgical programs.

The take-home message is that creating a "culture of safety" within an institution, especially within an ICU, appears to be more important than selecting which set of methodologies is used to effect change. Understanding a program's care processes at the ground level, which includes a questioning and honest examination of adverse events, is more critical than whether one employs lean processes with PDCA (plan-do-check-act) or the Institute for

Creating a "culture of safety" within an institution, especially in an intensive care unit, appears to be more important than the selection of which set of methodologies is used to effect change.

Healthcare Improvement methodology for rapid cycle improvement with PDSA (plan-do-study-act) or a comprehensive unit-based safety program process of learning from defects.

50.5 Safety-Related Outcome Measures: Improving Quality by Prevention of Adverse Events

As noted in the IOM definition of quality, safety is one component of quality. Safety performance (i.e., preventing complications that lead to morbidity or mortality) is an outcome that is important to patients and their families. Providing safe care often helps avoid costs, which increases value for the patient/family. As noted below, prevention of central line-associated blood stream infections (CLABSI) and catheter-associated urinary tract infections (CAUTI) are often monitored outcome measures that are suggested to reflect unit performance. To reduce these adverse events, compliance with central line insertion and care bundles and compliance with urinary catheter care bundles are often monitored as process measures (i.e., bundle compliance is assumed to result in the important outcome to patients of avoiding a catheter-related infection). Although process measures are relatively easy to measure and track over time, standardizing and measuring processes do not guarantee standardized high-quality outcomes since providers following identical guidelines achieve different results. There are likely several reasons for variation of outcomes, but one identified reason is that not all providers take the process seriously.

In the absence of true outcome measures, process measures are sometimes used as a surrogate to evaluate quality of care, and these process measures may be associated with reimbursement.

Since outcomes are often difficult to measure, payers, including Medicaid, have used compliance with process measures as a surrogate for quality and linked process compliance to reimbursement. These process indicators are well-meaning and may be logically, though indirectly, related to good outcome, but they do not accurately represent the attentiveness and decision-making that comprise superior care. An analogy for the use of process rather than outcome measures would be if rather than have students pass carefully prepared tests to assess whether they had mastered important material, we merely documented the process measure that they appeared to study with the book open for a number of hours in the preceding days.

The rate of accidental endotracheal tube dislodgment has been an indicator of quality of care since the initiation of PICUs.

In the pediatric critical care setting, the three most commonly reported safety-related outcomes are the rate of accidental extubation of intubated patients, CLABSI rate, and CAUTI rate. The first of these measures is clearly related to attentiveness and safety in care and is likely to affect patient outcome. The second is also clearly related to attentiveness and safety in providing care, but its tie to reimbursement has fostered an environment of data manipulation toward the end of avoiding a financial penalty. Since the presence of a documented CAUTI without symptoms is still considered an adverse patient outcome, the value of tracking this complication has been questioned. Furthermore, some institutions have developed care protocols to avoid CAUTI detection and made care decisions that may result in inadequate patient monitoring.

50.5.1 Accidental Extubation

The rate of accidental endotracheal tube dislodgment has been regarded as an indicator of quality of care since the initiation of PICUs. As a fellow in the 1980s, I still vividly recall our unit director assert that “self-extubation is a

failure of pediatric intensive care." This philosophy highlights one of the fundamental differences between adult and pediatric critical care since children cannot be convinced to tolerate procedures or discomfort through reasoned explanation alone. Thus, cooperation with care is the exception and not the norm. Pediatric critical care providers, physicians, nursing staff, and respiratory therapists are responsible for not allowing dislodgment of vital tubes and lines that could quickly compromise patient survival. The focus on accidental extubation has been a positive one.

Firstly, an accidental extubation event is defined as any episode where an endotracheal tube is removed without the specific intent to do so by the healthcare team at that moment. Thus, the child who is awakening from sedation or anesthesia and pulls his/her tube minutes before the healthcare team is set to remove the tube has been accidentally extubated. If one is serious about safety, then the healthcare team must always be in control of the endotracheal tube. Secondly, in quantitating the incidence, only "intubated patient days" and not all "ventilated patient days" should be counted in the denominator. For many PICUs, patients with a tracheostomy tube airway may represent a sizeable proportion of the ventilated patient days; these ventilated patients should not be included in the denominator. Finally, intubated patient days should constitute 24-h periods or their approximation. Thus, a patient intubated on Monday and extubated on Tuesday is one intubated patient day. If one extracts ventilated patient days by respiratory care charges, the above scenario would likely be counted as two charged days. Ideally, the intubated patient days should be derived from a PICU database where the initiation and termination dates and duration of intubated mechanical ventilation are recorded.

Initial reported incidences from single institutions in the 1990s ranged widely from 0.11 to 2.6 per 100 intubated patient days. Efforts to reduce the rate of unplanned extubations resulted in development of sedation scales to numerically quantify the degree of sedation to use as sedation targets to guide nurses in the timing of supplemental doses of sedation. At our institution, we demonstrated a decrease in accidental extubation rate from 0.59 to 0.11 per 100 intubated patient days (81% reduction) with the initiation of a standardized sedation goal algorithm. Another study demonstrated a relationship between nursing staffing ratio and the risk of unplanned extubation, though rates were quite high during this study (0.94 per 100 intubated patient days). Other approaches to reduce the rate of accidental extubation include standardized sedation order sets and standardized techniques for tube securing.

The goal should be for the rate of accidental extubation events, which require reintubation or resuscitation, to approach zero.

Most recent multi-institutional reviews report rates that vary from 0.29 to as high as 2.59 per 100 intubated patient days. These rates remain too high in my opinion. Despite the focus on this safety issue and efforts to develop care processes to reduce these potentially serious accidents, there remains much more that can be done. More rigor could be applied in evaluating each of these important safety events since all accidental extubation events are not the same. Each event also should be evaluated with reference to the risk imposed on the patient, such as differentiating between the accidental extubation event that occurs just prior to a planned extubation in a child with little or no residual lung disease and who remains extubated and the accidental extubation of a child with advanced lung disease who becomes promptly and dramatically hypoxemic, requiring immediate lifesaving intervention. A recent large series reported a reduction from a rate of 0.98 to 0.37 per 100 intubated patient days over the study period; 57% of events required positive pressure ventilation, and there were adverse consequences in 53% of events, including cardiac arrest (2%), bradycardia (11%), and stridor (14%). The goal should be for the rate of accidental extubation events that require reintubation or resuscitation to

approach zero. To compare outcomes across units, it is disappointing that two recent reports on the incidence of accidental extubation used "ventilator days" as the denominator, instead of the correct denominator of intubated patient days. The Society of Critical Care Medicine and the Children's Hospital Association could do more, both to encourage reduction in accidental extubation events as a safety goal and to require more consistency in measurement and reporting.

50.5.2 Central Venous Catheter-Related Blood Stream Infection

There is clinical decision-making tension between the recognized utility of central venous access catheters and the risk of catheter-associated bacteremia and sepsis.

Bloodstream infection secondary to central venous catheter use has been recognized as a serious concern for decades. Thus, there is clinical decision-making tension between the recognized utility of central venous access catheters, which provide secure access to the vascular system, a route for safe infusion of potentially caustic materials, and a site for central venous oxygen saturation monitoring, and the risk of catheter-associated bacteremia and sepsis with the potential for increased cost, morbidity, and mortality. In the late 1970s, Dennis Maki and others demonstrated that contamination of the insertion site with ingrowth of bacteria along the intracutaneous tunnel was the most common source of central venous catheter-associated bacteremia and sepsis. Semiquantitative culture of the intracutaneous sections of removed catheters was used to identify catheter-associated infections. Most central venous catheter-associated sepsis events were associated with documented infection of the insertion site. The accepted nomenclature for describing infections related to central venous catheters reflected this pathophysiologic understanding. Positive blood cultures drawn from central venous catheters but unassociated with significant symptoms were referred to as "contaminated hub" cultures and regarded as insignificant since very few catheter-associated sepsis events were felt to be related to the infusate. True CLABSI events were symptomatic and associated with positive quantitative culture of the intracutaneous portion of the removed catheter. Strategies aimed at reducing the rate of CLABSI-associated sepsis included routinely changing central venous catheter sites, as frequently as every 3 days; exchange of catheters over a wire at the same site, despite conflicting data as to the efficacy; and the use of antiseptic-impregnated catheters. Routine semiquantitative culture of the intracutaneous segment of removed catheters became a quality monitoring tool with published rates (2005) for catheter site colonization of 16.9% for non-antiseptic bonded catheters.

In 2006, the Children's Hospital Association initiated a collaborative to reduce the incidence of CLABSIs in children.

In the 1990s, Maki and others showed that chlorhexidine-based products provided a much more effective site barrier to antimicrobial growth (cutaneous antisepsis) than the previously employed povidone-iodine-based agents; subsequently, the rates of site infection and catheter-related sepsis fell with the use of these products. Most CLABSI-associated sepsis events are no longer derived from infection at the insertion site; instead, they are related to accessing the lumens for everything from blood drawing to blood product and medication administration. Thus, routine monitoring of semiquantitative cultures of removed central venous catheters is no longer done.

In 2006, the National Association of Children's Hospitals and Related Institutions (NACHRI, now Children's Hospital Association, CHA) embarked upon a collaborative to reduce the incidence of CLABSIs in children. The collaborative enlisted multidisciplinary teams from each participating PICU. The baseline data for the approximately 30 participating PICUs was 5.5 CLABSI per 1000 catheter days. Within the first year, ending December 2007, the aggregate rate fell to 3.0 CLABSI per 1000 catheter days (45% reduction). The

approach incorporated care bundles (i.e., process measures) based on available literature demonstrating a likely impact on CLABSI rates. The collaborative began with a protocol for catheter insertion, called the "insertion bundle," which was rolled out to all institutions and required training and ongoing audits at each participating institution. Subsequently, a "maintenance bundle" for ongoing care of central venous catheters was implemented at participating institutions. By the end of the third year, the CLABSI rate fell to 2.3 per 1000 catheter days (~58% reduction from baseline). There was no additional benefit from the use of chlorhexidine-impregnated sponges at site dressings. The widespread adoption of standardized insertion and maintenance care bundles constituted the most dramatic contribution to the reduction of CLABSIs in children.

There are varying costs reported in association with a CLABSI in children. One pediatric study estimated the cost of CLABSIs using the National Inpatient Sample databases from the Healthcare Cost and Utilization Project. Propensity score matching was based on patient characteristics and individual clinical classification diagnoses. Physiologic variables known to affect severity of illness and risk in ICU patients were not available. The estimated cost for one CLABSI was ~$48,000. Another pediatric study performed within one ICU matched numerous variables, including physiologic score, and derived an estimated cost of $33,000 with the Pediatric Risk of Mortality (PRISM) II scores just slightly higher in the group who had a CLABSI. The difference in PRISM II score prior to the onset of bloodstream infection was small, representing approximately a 3% absolute increase in risk of mortality. This appears to be the best controlled study in children.

Another pediatric study from a single cancer center utilized propensity score matching for pediatric oncology patients and derived a cost of a CLABSI to be ~$69,000. This analysis of one study center's database used only primary oncologic diagnoses without including physiologic variables in propensity scoring. It is my observation that the children most seriously affected by CLABSIs are those oncology patients during induction or relapse having impaired immune barriers with pancytopenia, mucositis, and often typhlitis. CLABSIs may not be preventable in some of these children since infections may arise from transmucosal invasion as well as from accessing the catheter ports. While the absolute values for costs of treating CLABSIs in children can be debated, it is clear that these events incur considerable additional length of stay and expense though rarely fatal. In addition, no study has addressed the overall cost of care and morbidities associated with a CLABSI (i.e., costs associated with managing morbidities following the ICU stay).

The costs of treating CLABSIs in children can be debated, though it is clear that these events incur considerable additional length of stay and expense though rarely fatal.

The largest study of the use of chlorhexidine bathing in children demonstrated no significant reduction in CLABSI rate in either the intention to treat or per protocol analysis with a weaker effect in the per protocol group.

The desire to qualify for financial reward from payers in response to lower CLABSI rates has promoted some interesting behaviors. Some institutions developed creative rationales for not counting infections. At least one institution decided to never draw routine blood samples from central venous catheters in their PICU so that all positive blood cultures in patients with a central venous catheter would not be considered a CLABSI event. Thus, to report lower rates, they subjected their patients to the discomfort of peripheral sticks for blood sampling which likely misrepresents the source of bloodstream infections. Fortunately, the new standards for diagnosis of CLABSI published by the National Healthcare Safety Network (NHSN) eliminated the finding of a single positive blood culture for a common commensal organism as a criterion for CLABSI. This reduced institutional anxiety over single contaminated blood cultures.

Another interesting phenomenon is embracing the use of midline catheters, which are catheters placed in the upper arm terminating outside the thorax. They can be placed in adolescents and adults but are largely not available for

small children. These catheters are more prone to serious thrombophlebitis secondary to infusing irritating medications, but do not count as central lines according to the NHSN and thus were embraced by many adult care hospitals to prevent CLABSIs. A midline catheter-related blood stream infection event doesn't count against the institution's financial reward or penalty. Making a distinction between one form of intravenous catheter therapy-related bloodstream infection and another ignores the fundamental goal of avoiding adverse outcomes that matter to patients.

Finally, the use of daily chlorhexidine bathing for children was embraced to reduce the incidence of CLABSI despite conflicting adult evidence and no evidence of CLABSI reduction in pediatric studies. The single largest pediatric study included five PICUs using a cluster-randomized crossover design. The study found no significant reduction in CLABSI in either the intention to treat or per protocol analysis with a weaker effect in the per protocol group. There was an inordinately high incidence of contaminated blood culture samples (11% of all positive cultures were in children with no CVL), with nearly 50% of isolates in the control group being coagulase-negative *Staphylococcus*, rendering suspect the conclusion of decreased non-CLABSI bacteremia. The authors conducted additional analysis after removing the contaminated cultures from the group with no central venous catheter but made no effort to remove the likely contaminated cultures, growing similar organisms, in children with central venous catheters. The authors are to be commended for attempting to address this important issue, but there are considerable challenges to testing interventions designed to decrease healthcare-associated infections. Additionally, small studies demonstrated low-level absorption of chlorhexidine into the bloodstream not only in premature infants but also in critically ill children with intact skin. The use of chlorhexidine bathing needs to be revisited weighing critically evaluated benefit versus potential harm.

The financial incentives to manage CLABSI rates have led to workarounds and modifications in care to minimize detection.

Although tracking the CLABSI rate appears to be an objective measure of unit performance, the rate may be misleading. Most CLABSI reduction bundles include early removal or avoidance of central venous catheters. Thus, the central line utilization rate has declined across most units. Since the rate is measured per 1000 catheter days, the absolute number of CLABSI events in a PICU may decline, but if the central line days decline by a greater proportion, the calculated rate will be higher. This penalizes units working to remove or avoid central venous catheters. The Solutions for Patient Safety collaborative tracks central line utilization as well as the CLABSI rate, but payers and regulators often focus only on the CLABSI rate.

In conclusion, catheter-associated bloodstream infections constitute an important complication in the management of seriously ill children, resulting in significant short-term morbidity and increased length of stay and cost. Collaborative efforts to reduce the rates of CLABSI in children were quite successful and contributed greatly to the safe care of children. However, we must be vigilant to not acquiesce to institutional decisions distorted by financial incentive, which may place patients at risk for adverse short- or long-term outcome, and we should recognize the potential limitation of tracking the CLABSI rate without considering the impact of reduced central line days.

50.5.3 Catheter-Associated Urinary Tract Infection (CAUTI)

Positive urine cultures in patients with an indwelling urinary catheter is a component of the NHSN quality measures. It is recognized that urinary catheters over time become colonized with bacteria, likely migrating up the urethra. It is also well accepted that undetected urinary tract infections progressing to sys-

temic infection are a significant source of morbidity and indeed mortality in elderly or debilitated patients. Thus, because serious systemic infection is a potential harm from long-term indwelling urinary catheters, it has become a national safety goal. It is from the experience in adult medicine that the focus on reducing CAUTIs has become a pediatric quality measure.

It was common practice in critical care settings for patients who required urinary catheters to obtain surveillance cultures periodically to detect early colonization prior to the onset of more serious systemic infection. The detection of low-level urinary colonization in these patients afforded the care team the opportunity to address the issue in several ways, most commonly to remove the catheter for a short period of time and reinsert following the clearing of the urine. Unfortunately, the patient safety goal requires but a single temperature of >38° to differentiate between colonization and invasive infection. Therefore, the surveillance culture monitoring to safely employ continuous urine output monitoring without developing invasive infection can no longer be performed without suffering financial penalty for detecting bacteriuria. Thus, like with CLABSI, financial incentives led to work-arounds and care modifications to minimize detection. One such modification is for units to effectively ban urine cultures in patients with urinary catheters. In those units, patients with urinary catheters who develop fever have the catheter removed and are placed on a short course of antibiotics with no culture obtained to avoid the penalty of detection.

Additionally, it is now not uncommon for patients with or who develop acute kidney injury to not have a urinary catheter placed and therefore may not have timely assessment of the adequacy of resuscitation and establishment of urine flow. Numerous studies from approximately 2000 onward demonstrated that while CAUTIs may constitute a reservoir of antibiotic-resistant organisms in the hospital, they are rarely symptomatic, and often there is infection at another site constituting a risk factor for the development of CAUTI. Most recently, a large study (137 adult ICUs in 65 hospitals) demonstrated that with the 2015 revision of the NHSN definition of CAUTI, the CAUTI incidence fell by 44% but there was a concomitant 30% increase in the incidence of CLABSI, simply due to reclassification of positive blood culture events as CLABSI since they could no longer be labeled as CAUTI due to the mandated change in the interpretation of the presence of similar bacteria in the urine.

In January 2019, the Centers for Disease Control published guidelines and reporting forms for both adult and pediatric ventilator-associated events (VAE).

Like tracking CLABSI rates, CAUTI rates are also impacted by a reduction in urinary catheter utilization, the denominator in the rate equation. As catheter use is avoided or urinary catheters are removed more quickly, the CAUTI rate may increase in a PICU even with no increase or an absolute decrease in the number of CAUTI events per 100 bed days, for example.

50.5.4 Ventilator-Associated Events

The development of a new pulmonary infection in mechanically ventilated patients within the ICU (ventilator-associated pneumonia or VAP) has long been recognized as a significant source of morbidity and increased mortality in critically ill adults. Interventions aimed at prevention were studied and adopted with the hope of positively affecting outcome in mechanically ventilated patients. Complicating the identification of VAP is the observation from numerous studies that many asymptomatic patients have positive bacterial cultures of respiratory secretions. In addition, antibiotic therapy is not uniformly successful in eradicating even sensitive organisms from the respiratory secretions of ventilated patients, and antibiotic use may alter the flora in the mouth and GI tract. Criteria had to be developed that were not only sensitive enough to detect clinically important infections but specific enough to ignore the back-

ground noise of positive tracheal bronchial cultures from colonization in patients with instrumented airways.

Prior to 2013, the surveillance for ventilator-associated infections was limited to pneumonias, which required a new radiographic infiltrate in addition to signs of impaired oxygenation and systemic inflammation. Since 2013, it was recognized that other levels of infection, most notably tracheobronchial infection (ventilator-associated tracheitis, VAT), are even more common, though associated with less morbidity and potential for mortality. In January 2019, the Centers for Disease Control published guidelines and reporting forms for both adult and pediatric (► https://www.cdc.gov/nhsn/pdfs/pscmanual/pedvae-current-508.pdf) ventilator-associated events (VAE). As the criteria and nomenclature to describe adverse infectious occurrences in ventilated patients continuously evolved, several studies attempted to critically evaluate both the completeness of surveillance and the effectiveness of measures aimed at VAE prevention.

Recent studies demonstrated that certain components of VAP prevention bundles, such as head of bed elevation, sedation infusion interruption, spontaneous breathing trials, and thromboembolism prophylaxis, appear to be effective.

Over the past decade, the rate of VAP reported to the CDC declined. However, an analysis of patient safety events reported by hospitals in 80,000 Medicare patients hospitalized with 1 of 4 conditions between 2006 and 2012 identified 1856 intubated and ventilated patients over this 7-year period which revealed no change in VAP rate (~10 VAP per 100 ventilated patients). The PALISI Network undertook a multicenter point prevalence study to identify both the diagnoses assigned by physicians and antibiotic prescribing behavior as well as examine these decisions in the context of the new diagnostic criteria. They noted that positive respiratory cultures appear to be the primary determinant of continued antibiotic treatment in children with suspected ventilator-associated infection. The presence of positive cultures was not associated with outcome. Perhaps more significantly, the new CDC diagnostic criteria identified only 6% of subjects who were felt by their physicians to have a VAE. This observation questions the utility of the proposed pediatric ventilator-associated event (PedVAE) criteria.

There is no effect on the development of ventilator-associated infections from the adoption of in-line closed suctioning.

If the incidence of VAP has not declined in adults, what about the incidence of interventions to prevent VAP? Institutions developed and implemented VAP prevention bundles over the last 15 years. Recent studies demonstrated that certain components of VAP prevention bundles, such as head of bed elevation, sedation infusion interruption, spontaneous breathing trials, and thromboembolism prophylaxis, appear to be effective. However, other practices such as daily oral care with chlorhexidine and stress ulcer prophylaxis appear to be harmful. In randomized controlled trials, spontaneous awakening and spontaneous breathing trials are associated with a decreased duration of mechanical ventilation and ICU length of stay. Interestingly, in a meta-analysis of randomized controlled trials, oral chlorhexidine was associated with lower VAP rates but increased mortality. A similar evaluation of stress ulcer prophylaxis showed either no benefit or an increased incidence of VAP. A Cochrane review observed that head of bed elevation decreased VAP rate but not duration of mechanical ventilation. Subglottic secretion drainage appears to have no effect on VAP rates. Interestingly, a Cochrane review observed a benefit for probiotics on VAP rate but not on any other outcome measure. Finally, there is a strong signal for VAP prevention from selective gastric decontamination. This is practiced widely in Northern Europe where it also was demonstrated to lower 28-day mortality and to not significantly increase the population of resistant organisms. This practice has not gained favor in North America due to concern for already high levels of antibiotic resistance.

Discussion of VAEs would not be complete without mentioning closed in-line suctioning. Discontinuation of open suctioning in favor of in-line suctioning was promoted and widely accepted starting about two decades ago. It was hoped that it would prevent contamination of the respiratory system by avoiding opening the system and inserting catheters from the outside. Unfortunately,

studies failed to demonstrate an effect of in-line closed suctioning on the development of ventilator-associated infections. It is clear, however, that closed suctioning is less stressful to the patient than open suctioning. In patients requiring high levels of support, there is less transient decrease in lung volumes, and in patients with cardiovascular disease, there may be less transient hemodynamic changes. However, observations during flexible bronchoscopy in ventilated patients demonstrate that disconnection of the ventilator circuit causes brief lung de-recruitment with movement of secretions to the carina where they are easily aspirated. Conversely, during bronchoscopy when patients remained ventilated, secretions remain in the distal airways.

It is our experience that in selected patients who are not improving on the ventilator with diffuse rhonchi, the use of open suctioning to allow transient de-recruitment and access to secretions followed by recruitment causes a prompt and predictable improvement in pulmonary function. Anecdotally, I am impressed with the frequency patients are referred for higher-level pulmonary care due to deteriorating status secondary, largely, to fear of suctioning. One of the most satisfying bedside experiences in pulmonary toilet is disconnecting a patient from the oscillator, followed by suctioning a massive quantity of retained secretions, then re-recruiting with a few breaths, and placing the patient back on the oscillator with the result of seeing the best arterial blood gases in many days. There is no reason to fear de-recruitment as physiologic studies demonstrate re-recruitment can be accomplished with a few breaths. At our institution, virtually all patients intubated with significant lung disease have a standing order for periodic open suctioning, with assisted passive cough if paralyzed at the time of suctioning, for the express purpose of removing retained secretions.

50.6 Measurement of Outcomes in Pediatric Critical Care Medicine

While monitoring compliance with process measures as surrogates for outcomes has grown, ultimately, the goal is to measure outcomes that matter to patients and their families and gage the effectiveness of care in the pediatric intensive care unit. These outcome measures include standardized mortality ratios, based on severity of illness-predicted mortality algorithms, risk-adjusted mortality for congenital heart surgery, risk-adjusted evaluation of long-term morbidity (i.e., functional outcome) following critical illness, and cost and length of stay evaluations by diagnosis-related groups.

50.6.1 Risk Adjustment

The outcomes achieved in the PICU depend to some degree on each patient's initial conditions (i.e., risk factors). Increasingly, children admitted to the PICU have one or more preexisting condition that can affect both the treatment plan and the likelihood or degree of success. For example, a child may be admitted for treatment of acute leukemia or may be admitted for treatment of refractory, relapsed leukemia. The diagnosis is "leukemia" in both cases, but the outcome is likely to be different between the two children. Outcomes should be adjusted for the patient's initial conditions to allow fair comparisons across patient populations. Measuring and adjusting for these risk factors (at least to the extent they are known) is important when comparing, interpreting, and improving outcomes. For example, new data suggests there are several different

genetically determined phenotypes of response to sepsis. In the future, we may be able to adjust risk for these phenotypes to identify the most effective therapies for each one.

Failing to risk-adjust can lead to unintended consequences from publicly reported outcomes. For example, simply reporting survival following cardiac surgery in children would lead one to believe that the largest medical centers have worse outcomes. This is why it is important to adjust the mortality data for the patients' Risk Adjustment for Congenital Heart Surgery (RACHS) score or other severity-based adjustment. Adjusting for risk is not only important to measure outcomes accurately, but it is also essential to understand the link between risk factors and specific patient health outcomes so that improvement may be achieved.

Finally, risk adjustment is essential not only for making comparisons but also to mitigate the risk that health systems or providers will "cherry pick" healthier patients to improve their reported outcomes. Inadequate risk adjustment and poor understanding of actual costs, especially for medically complex patients, are a major cause of underpayment of providers and health systems for managing patients with complex conditions, which may encourage some health centers to avoid caring for these patients.

Adjusting for initial conditions or risk typically involves two approaches. One stratifies patients based on the most important known risk factors to allow outcomes to be compared. This is the methodology used in the RACHS system that classifies children with congenital heart disease based on their anatomic diagnosis. The other approach utilizes regression analysis to calculate expected outcomes based on risk factors significantly associated with the outcome of interest, such as physiologic parameters. This approach is used with the Pediatric Risk of Mortality (PRISM) and Pediatric Index of Mortality (PIM) scoring systems.

Both methods depend on having sufficiently large patient populations to support statistically meaningful comparisons. To accumulate adequate patient numbers, it may be necessary to aggregate patients over multiple years, such as done when evaluating outcomes following organ transplantation or complex congenital heart disease repair.

As noted, both methods depend on identifying important risk factors, which has improved over time but is still imperfect. As noted above for sepsis, besides traditional physiologic measures such as blood pressure and lactate, there are likely genetic factors modifying the patient's stress response that we are just beginning to identify. Similarly, physiologic-based risk adjustment often does not account for the presence of underlying conditions that can influence outcome. For example, the PRISM score was developed and works well to adjust for risk in a *generalized PICU population* but may not work as well for specific groups of patients.

50.6.2 The Virtual PICU and the Use of PICU Mortality Prediction Tools

The virtual pediatric intensive care unit (VPICU) was developed to create a common information space for providers of pediatric critical care.

The virtual pediatric intensive care unit (VPICU) began in 1998 with a gift from the LK Whittier Foundation. Its mission is to create a common information space for pediatric critical care providers. Development of a broad multi-institutional PICU patient database began in 2002. The program rapidly expanded with recruitment in early 2004 at the PALISI meeting, which was funded in part by the National Institutes of Health with administrative support provided through the Children's Hospital Association (CHA).

The first demographic and outcomes comparison data that our institution received was for the 1-year period from July 2004 to June 2005 and included over 31,000 patients from 32 other institutions in the comparison group. Since then, the data set has expanded in size and scope. Just 3 years after the broad invitation for membership, virtual PICU (now known as virtual PICU system, VPS) boasted 67 participating institutions. The VPS is a partnership between the Children's Hospital of Los Angeles and CHA supported by grants and membership fees, providing a large database from participating North American pediatric critical care units. By 2008, some member institutions began submitting PRISM III data but far less than 100% participation. Starting in 2009, there were enough institutions submitting PRISM III data to risk adjust the mortality assessment using the PRISM III score. The common reporting metric is the standardized mortality ratio (SMR), which is the ratio of the number of observed to predicted mortalities for a population of patients. When the 95% confidence intervals of the SMR are <1, it denotes a significantly superior risk-adjusted survival rate, whereas if the 95% confidence interval is >1, the unit has a significantly worse survival rate.

The two primary scoring systems for risk of mortality in the pediatric population are the Pediatric Index of Mortality (PIM) and PRISM.

The two primary systems for estimating the risk of mortality in children are the PIM and PRISM scores. The PRISM score was developed in the early 1980s and included an assessment of chronic disease state in addition to 34 acute physiologic variables recorded over the first 12 and 24 h following PICU admission. By 1996, the PRISM risk scoring system was updated to PRISM III and was used nationally as an outcomes comparison tool, with more than 30 PICUs enrolled and participating in the outcomes evaluation system, PICU Evaluations (PICUEs). The most recent refinement, PRISM IV, was completed in 2015. The number of acute variables was refined to 17, which are collected beginning 2 h prior to PICU admission to 4 h after admission for laboratory variables and in the first 4 h of PICU care for physiologic variables. PRISM remains the most robust and accurate system to estimate mortality risk in children.

PRISM remains the most robust and accurate scoring system to estimate mortality risk in the pediatric population.

The PIM score was developed in Australia in the late 1990s based on the assumption that scores using predictor variables recorded over 12–24 h will invariably assign more points to patients who are initially mismanaged and, thus, whose physiologic variables deteriorated into ranges associated with a higher score. For this reason, the developers chose to score patients based on their physiologic state only within the first hour of admission to the PICU. The PIM score is attractive because of its limited number of variables and time frame for data collection, reducing the costs of data collection and entry. Indeed, funding for staff to collect and enter PRISM data has been an obstacle to the broad inclusion of PRISM data in the VPS database. PIM was updated in 2013 to PIM 3 based on data from Australia, New Zealand, Ireland, and the United Kingdom. Unfortunately, the same simplification in the data collection process using basic variables (e.g., any respiratory support, assignment of the patient to a high-risk diagnoses or not) and shortened data collection period resulted in a system that appears less robust and accurate than the PRISM algorithms.

Ongoing refinements and recalibrations, with exclusion of non-predictive ranges and variables, resulted in a robust predictor of mortality for the large VPS database. Indeed, for the reference group of 278,000 patients included in our most recent quarterly report comprising the last 11 quarters, the SMR by PRISM III was 1.0 (observed = predicted), whereas the reference group SMR was 0.93 based on PIM 2. This has been a consistent finding over years: PRISM-based SMR for the large reference sample approximate 1.0, whereas PIM 2-based estimates consistently overpredict mortality resulting in a lower

Virtual PICU's primary strength to date has been allowing member institutions to compare their mortality outcomes with reference groups.

SMR. PIM 3 data collection was added to VPS in 2014, but its predictor coefficients did not calibrate well with the VPS database requiring recalibration by VPS to what is now called the PIM 3 North America model. Following this recalibration, it performed better than PIM 2 with reference group SMR of 1.02 for the 278,000 patients reference group. However, it appears that in seeking simplicity, PIM assigns mortality risk to some rather broad, less discriminatory parameters such as the assignment of "high-risk diagnoses" and whether or not invasive or noninvasive respiratory support was chosen preadmission to the first hour following admission. VPS abandoned PIM 4 mortality risk estimation after 2018 and began reporting outcomes using PRISM IV algorithms for patients enrolled during and after 2018.

Virtual PICU's primary strength to date has been allowing member institutions to compare their outcomes with reference groups. Besides SMR, periodic reports include readmissions within 24 h, a host of demographic variables regarding referral sources and discharge destinations, distributions of admissions by diagnosis categories, and acuity-adjusted length of stay. More recent additions include examination of end-of-life variables, mortality by length of stay, mortality by most common diagnosis groups, bar graphs of unit ranking according to SMR, and other outputs. Unlike the outcomes database administered by the Society for Thoracic Surgeons and the American College of Cardiology, the VPS system does not allow member institutions to see other unit's data.

Early versions of PIM significantly overpredicted mortality for the subset of "scheduled admissions."

The VPS system allows creation of personalized reports, through a portal known as My VPS. One can attempt to mine the database for insights into the functioning of one's PICU by running small personalized reports, comparing the unit to a reference group defined by a number of different variables such as units with and without fellowship programs, units with and without transplant programs, units performing or not performing ECMO, number of PICU beds, and even number of PICU attending physicians on the team. After defining a reference group, the data mining tool permitted comparison based on patient characteristics such as scheduled versus unscheduled admission, length of stay, and diagnosis categories among other variables. Thus, one could access a report looking at the mortality outcomes for all unscheduled admissions and length of stay greater than 7 days to examine one's SMR in comparison with the reference group of all other units with ECMO capability, focusing on late death. One disadvantage of the personalized reports available through the "My VPS" portal was that all reported SMRs used only the PIM 2 mortality predictor algorithm.

Using the customized query platform, one could make several interesting observations, lending themselves to insight and perhaps further inquiry. For instance, we noted that PIM 2 appeared to dramatically overpredict mortality for the entire subset of "scheduled admissions," such that the large reference sample SMR for all scheduled admissions was as low as 0.60 during reporting periods. Since units vary in the percentage of scheduled versus unscheduled admissions, this bias in the mortality tool tended to favor units with a greater percentage of scheduled admissions. For this reason, if one wanted to produce a valid comparison report for their PICU versus other PICUs, it was prudent to limit the report to unscheduled admissions. Limiting one's query to only unscheduled admissions was attractive also from a phenomenological perspective, in that practitioners understand that they are most tested by the unanticipated critically ill child presenting during the most inconvenient times of the day.

Another interesting observation we made concerned analyzing mortality in patients in the PICU from 0 to 7 days or greater than 7 days. The disease processes associated with early versus late mortality are somewhat different, though they clearly overlap. For instance, catastrophic brain injury with evi-

dence of brain death on admission is almost uniformly a highly predictable mortality within the first 7 days, though there could be circumstances when the process takes greater than 7 days. Not only are the disease processes different in short-stay versus longer-stay patients, but the skills for early resuscitation and stabilization are different from the knowledge and skills required to manage the critically ill child through a protracted recovery. If a unit's SMR for patients in the ICU greater than 7 days significantly exceeds the reference sample, one could argue that the unit experiences significant numbers of highly predictable deaths occurring beyond the 7 days' cutoff. However, that would likely be reflected in a significantly lower SMR within the 0–7 days' patient population. Thus, if the unit's reported SMR was equal to the reference group for the shorter-stay patient but exceeded the reference group for the longer-stay patient, then there may be something that unit could learn about the facilitation of organ recovery during protracted critical illness. Likewise, if a unit or group of units demonstrates an SMR equal to or lower than the reference sample within the first 7 days and clearly superior SMR beyond 7 days, then these units could be evaluated to identify best practices, such as nutritional and immune reconstitution and support of organ recovery.

Finally, years ago we observed that the SMR was significantly higher for larger units, especially units with greater than eight PICU attendings. Looking at only unscheduled admissions, we noted that for the entire reference sample of 80,000 patients, the unscheduled admission SMR was 1.02 by PIM 2. Analysis by unit faculty size showed the SMR was 1.11 for the 28,000 patient sample in units with >8 PICU attendings and was 0.96 for the 52,000 patient sample in units with ≤8 PICU attending physicians. Drawing specific conclusions is not possible based on a univariate analysis of a database employing complex multivariate predictors of mortality. When we made this observation, we inquired about access to the blinded raw database, which was not available. It would be interesting to analyze the raw data, adding this one additional variable in a multivariate multiple regression model using PRISM IV algorithms to ascertain whether the attending physician program's size is independently associated with outcome. This illustrates the potential power of such a large database.

Although the risk-adjusted SMR permits some level of comparison between units, the limitations of currently available risk adjustment methodologies should be recognized, as previously detailed. The preceding examples of the effect of the proportion of scheduled admissions and the number of unit attending on the SMR illustrate these limitations. It is likely that currently available risk adjustment and SMR calculations work for large populations of patients likely based on balancing out these differences within the overall unit population. Furthermore, generalized outcomes, such as the SMR, do not identify the causal connections between specific care processes and outcomes since outcomes are influenced by many different care providers and the specific mix of medical conditions and interventions in the patients for whom care is provided.

When we were first asked at the 2004 PALISI meeting about our interest in participating in the virtual PICU enterprise, we hoped to use this mega-data to evaluate the effects of care paradigms on specific outcomes to answer questions such as the following: does the approach to hemodynamic support affect the incidence of acute kidney injury (AKI) occurring during critical illness, or does the timing of initiation of diuresis and attention to fluid balance affect the course of hypoxemic lung injury? Thus far, it has not been possible to mine the VPS database to ask those questions. Recent discussions, however, have been promising. Increasingly, unit directors are inquiring about transparency and sharing best practices. There is some commitment to develop regional practice sharing agreements within VPS.

Unit directors are inquiring about transparency and sharing best practices, and recently there is some commitment to develop regional practice sharing agreements within VPS.

50.6.3 The Society of Thoracic Surgeons Database

The Society of Thoracic Surgeons Congenital Heart Surgery Database (STS-CHSD) was founded in 1994 in an effort to track outcomes in support of quality improvement and patient safety.

In a joint venture between the Society for Thoracic Surgeons (STS) and the American College of Cardiology (ACC), a case registry was created to track outcomes, specifically discharge mortality for operative cases. The current registry encompasses databases for adult cardiac surgery, congenital heart surgery, and general thoracic surgery. Of interest to pediatric intensivists is the Congenital Heart Surgery Database. The STS Congenital Heart Surgery Database (STS-CHSD) was founded in 1994 to track outcomes in support of quality improvement and patient safety. Data submission ending June 30, 2018, included 4566 neonatal cases, 7676 infant cases, and 9747 childhood cases suitable for analysis within the STS-CHSD database.

The STAT scoring system divides pediatric cardiac surgical procedures into five categories based on the surgical complexity and thus operative risk.

Historically, there were three major multi-institutional efforts to develop risk stratification for congenital cardiac surgical operations:

1. The Risk Adjustment in Congenital Heart Surgery (RACHS) scoring system and the Aristotle Basic Complexity Score were developed when there were smaller multi-institutional data sharing associations.
2. The STAT (Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery) Mortality Score and Categories was developed based on an analysis of 77,000 operations performed between 2002 and 2007. The STAT scoring system divides surgical procedures into five categories of increasing complexity and risk. Category 1, the lowest complexity, includes ASD, VSD, and vascular ring repairs among other procedures. Category 2 includes the bidirectional Glenn operation, repair of coarctation of aorta, Fontan procedure, tetralogy of Fallot repair, and valve replacements among other procedures. Category 3 procedures include arterial switch operation, atrioventricular canal defect repair, right ventricle to pulmonary artery conduit replacements, and Rastelli procedures among others. Category 4 procedures include repair of double outlet right ventricle, interrupted aortic arch repair, systemic to pulmonary artery shunts, repair of total anomalous pulmonary venous connection, heart transplant, and truncus arteriosus repair among other procedures. Finally, category 5 procedures include the Damus-Kaye-Stansel procedure, Norwood procedure, and transplantation of heart and lung.
3. The STS-CHSD mortality risk model calculates an operative mortality rate for patients undergoing these procedures. Risk is stratified according to procedure and certain other patient factors including age, weight, prior cardiac operation, noncardiac congenital anatomic abnormality, chromosome abnormality, prematurity, preoperative mechanical circulatory support, shock at the time of surgery, mechanical ventilation prior to surgery, renal failure, preoperative neurological defect, etc.

Institutions earning a three-star STS rating are those where the observed to expected mortality ratio is significantly < 1.0.

The STS public reporting database includes cases encompassing the most recent 4-year period. For each institution, the observed and expected discharge mortalities within each of the five STAT categories and overall observed and expected mortality for the entire program are reported. An observed to expected ratio (similar to the SMR reported in VPS) is reported for each STAT category and overall for each institution along with the 95% confidence interval. Institutions are categorized into one of three levels of star rating. Institutions earning three stars are those where the observed to expected mortality ratio is significantly less than 1.0 (i.e., the 95% confidence interval is <1). Likewise, institutions earn one star if the observed to expected mortality ratio is significantly greater than 1.0 (95% confidence interval is >1). Most institutions earn a two-star rating when the observed to expected mortality ratio is not statistically different from 1.0. For the 2014 through 2017 4-year time

frame, there were 119 institutions in the STS-CHSD, with 12 institutions earning 3 stars, 85 with 2 stars, and 13 with 1. Interestingly, there is no significant relationship between surgical volume and the achievement of an observed to expected mortality ratio significantly <1.

50.6.4 Functional Outcomes and Morbidities Following Pediatric Critical Illness

Mortality is often used to assess quality, but that has become a relatively infrequent outcome (often <2.5%) of admissions. When the outcome is infrequent, it increases the need to collect data on large populations, increasing the cost and time required to obtain clinically meaningful data. Morbidity may be a more relevant and important measurement but is difficult to measure in the absence of consensus definitions. Morbidity is determined by the effects of the disease process leading to the need for PICU care, as well as the effects of the treatment itself. Besides obvious morbidity, such as AKI incurred during hospitalization, morbidity also includes changes in the functional status of the patient following PICU care, which is typically more difficult to measure.

Historically, three broad categories of methods were used to assess morbidity in critically ill children: (1) global measures, (2) health-related quality of life scales, and (3) adaptive behavior scales. Global measurements include the Glasgow Outcome Scale (GOS) and its pediatric versions, the Pediatric Cerebral Performance Category (PCPC), and the Pediatric Overall Performance Category (POPC). These scales assign a single value to classify the overall functional level without examining specific functional domains beyond the PCPC's focus on cognitive performance. The newer extended version of the GOS (GOS-E, which includes a pediatric version) uses a short structured interview with the patient or family to determine the functional status. The GOS-E is primarily used as an outcome for brain injury studies and categorizes children into two age groups in an attempt to account for developmental stages. The Approaches and Decisions in Acute Pediatric Traumatic Brain Injury Trial (ADAPT; ► https://www.adapttrial.org/) is using the pediatric version of the GOS-E.

In the 1990s, investigators at Arkansas Children's Hospital sought to develop two functional outcomes scales for children: the POPC and PCPC. Approximately 1500 consecutive subjects were assigned baseline POPC and PCPC scores on admission to the PICU and scored again at discharge from the hospital, demonstrating validity and interrater reliability. Subsequently, a prospective study collected PRISM score and other demographic data, seeking to identify predictors associated with a decline in POPC resulting from pediatric critical illness. These functional outcome measures were then applied to a multicenter sample, encompassing 16 PICUs across the United States. It was observed that mild baseline cerebral deficits in children were associated with 18% longer PICU stays and that moderate to severe deficits for both the POPC and PCPC score predicted 30 to 40% increased length of stay. Finally, deterioration in both scores from PICU admission to discharge was predicted by the PRISM score as well as PICU length of stay. Unfortunately, the POPC and PCPC scores lack both precision and reproducibility and only had a relatively weak, although statistically significant, association with long-term neuropsychological tests.

The most popular health-related quality of life (QOL) indicators are the PedsQL (► https://www.pedsql.org/) and the Child Health Questionnaire (CHQ; ► https://www.healthactchq.com/survey/chq). The former is a brief survey (23 items) that includes physical, emotional, social, and school func-

tioning; the score survey can be completed by either the child or parent-caregiver. The CHQ survey is for children from 5 to 18 years of age and is completed by the child or parent. These assessments are often subjective, leading to differences in scores when assessed by a parent, healthcare provider, and patient. Neither tool is specific to the PICU population, and there is no consensus as to the best method to use for post-PICU studies.

Adaptive behavior scales include neuropsychological and psychometric testing. They are commonly used for research and individual patient assessment and focus on skill domains important to normal functioning adjusted for the child's developmental age. The most commonly used scores are the Vineland Adaptive Behavioral Scale (VABS) and the Adaptive Behavior Assessment System (ABAS). Again, neither score is specific for post-PICU studies, but the VABS was used to compare 1-year good functional status following resuscitation from cardiac arrest.

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In 2009, a new pediatric outcome measure, the Functional Status Score (FSS), which is an adaptive behavioral scale, was developed by the Collaborative Pediatric Critical Care Research Network (CPCCRN).

The Functional Status Score (FSS) was developed in 2009 by the Collaborative Pediatric Critical Care Research Network (CPCCRN). The score was developed by a formal consensus process of pediatric health professionals from 11 institutions, encompassing diverse areas of pediatric care. The six functional domains selected include mental status, sensory functioning, communication, motor functioning, feeding, and respiratory status. The functional status for each domain was characterized from normal (score of 1) to very severe dysfunction (score of 5). Thus, FSS scores range from a best functional score of 6 to the most highly impaired score of 30. Within each domain, the investigators used the ABAS to validate and calibrate the FSS score. FSS scores are categorized as good (6–7), mildly abnormal (8–9), moderately abnormal (10–15), severely abnormal (16–21), and very severely abnormal (>21).

Compared with data from 20 years earlier, it appears that the PICU mortality rate decreased by approximately half but the rate of new morbidity increased by an equal proportion.

The FSS score was used in a prospective multicenter sample of >5000 critically ill children to investigate the occurrence of new morbidities associated with pediatric critical illness. Significant new morbidity was defined as a worsening of overall FSS score of 3 or more from baseline to hospital discharge. Mortality rate during the study was 2.4%, whereas the rate of significant new morbidity was twice as high at 4.8%. Significant new morbidity occurred in all FSS baseline levels of function. Of patients with new morbidities, 45% had a worsening of FSS level of 3 or greater within at least one domain. New morbidities occurred more frequently in infants but were present in all age groups. Compared with data from 20 years earlier, PICU mortality decreased by approximately half, but the rate of new morbidity increased by ~50% so that combined morbidity and mortality rate decreased minimally from 7.7% (mortality 4.6% and morbidity 3.1%) to 7.2% (mortality 2.4% and morbidity 4.8%). The morbidity measurement tool used in the historical cohort was different but comparable to the FSS.

Subsequently, in a prospective analysis of ~10,000 PICU patients at seven institutions, both morbidity (FSS score) and mortality were significantly associated with PRISM III score, in both dichotomous (survival and death) and a trichotomous (survival without new morbidity, survival with new morbidity, and death) models. Morbidity risk initially increased with increasing PRISM III score but decreased at the highest mortality risk levels as more mortalities replaced potential morbidities. Another observation was that physiological status had a stronger association with the risk of mortality than morbidity. Morbidity and mortality prediction differed in that having a cancer diagnosis and the baseline FSS score were significant, independent predictors of mortality, but not morbidity. Neurological disease was a significant predictor of only morbidity. Thus, in an age of decreasing mortality from critical illness, shifting focus toward new morbidity as a quality measure for pediatric critical care is

appropriate but requires more effort. The authors also noted more variability among the participating units with reference to standardized morbidity ratios than with the SMR. This likely represents the periodic recalibration and refinement of the PRISM to predict mortality.

Finally, the FSS was used to track functional outcome for up to 3 years post discharge in one PICU. Both mortality and morbidity increased after discharge; mortality rate increased from 3.9% at discharge to 7.8% at 6 months and 10.4% after 3 years. In addition, 10% of children exhibited functional improvement over time, whereas 44% showed no change in functional status and 38% demonstrated worsening of their functional status or died. This was a small sample and an exploratory study examining the feasibility of long-term follow-up for post-PICU morbidity but suggests that measuring outcomes that matter to patients following a PICU hospitalization may require long-term follow-up. Most of the children who later died had chronic life-threatening conditions, consistent with the observation that an increasing proportion of the children admitted to PICUs nationwide are medically complex and vulnerable.

More than two-thirds of children who stay in intensive care for greater than or equal to 28 days had an unfavorable outcome of moderate disability, severe disability, or death.

Researchers in Australia examined the outcomes at a single institution of long-stay (defined as >28 days) PICU patients over a 20-year period, ending in 2008. These long-stay patients accounted for 1% of all PICU admissions but utilized 18.5% of occupied bed days. In addition, the proportion of long-stay patients increased over the 20-year study period. At the time of follow-up, approximately 50% of the long-stay patients died, with 27% of the patients having good long-term functional outcome as defined by a modified GOS rating of normal functioning or mild disability. Overall, more than two-thirds of children who stay in intensive care for greater than or equal to 28 days had an unfavorable outcome of moderate disability, severe disability, or death. More recently, a small study of two Canadian PICUs observed that more than 40% of admitted patients had some functional limitations at baseline and 80% of all admissions experienced some functional deterioration following critical illness with two-thirds of patients having some functional recovery at 6 months.

With a greater proportion of PICU admissions comprised of children with long-term functional limitations, and with success in reducing mortality, acquired morbidity has become more common. Tracking functional outcomes requires significantly more administrative work than tracking risk-adjusted mortality rates but is necessary if we seek to provide the best possible service to the children entrusted to us. Utilizing the risk assessments identified by the abovementioned studies, we could start by focusing our long-term functional outcome tracking on those patients at most risk. VPS data demonstrates that most PICUs in the United States have patient populations with median risk of mortality well below 1% (i.e., may not need intensive care), so it may not be necessary to monitor functional outcome for that population. Limiting functional outcome tracking to patients with longer length of stay, longer duration of mechanical ventilation, and higher PRISM scores would reduce the administrative cost of implementing this important outcome monitoring.

Looking ahead, it is reasonable to expect that strategies aimed at nutrition and/or pharmacologic support for brain recovery could improve functional outcome. Indeed, a growing body of literature on nutritional support for brain recovery as well as neuroprotective strategies may provide a roadmap toward improving functional outcome. Furthermore, there is growing interest in the use of early mobilization in the pediatric ICU population, as is commonly done in adults, as a potential avenue to minimize neuromuscular disability following PICU stay.

50.6.5 Assessment of Cost and Length of Stay

Benchmarking by cost and length of stay can be used to develop more efficient care models.

Care of critically ill patients is expensive; 15–20% of adult hospital budgets are spent in the ICU; thus, intensivists increasingly are expected to focus on achieving quality outcomes at a reasonable cost. As previously noted, cost is an essential element of the value equation, but determining actual cost is challenging. Two sources for pooled comparison data for the pediatric critical care population are the University Hospital Consortium (UHC) and the CHA. Subscribing institutions submit data on each admitted patient, including all coded diagnoses, comorbidities, complications, and costs estimated from charges. The CHA database includes all admissions to participating children's hospitals, and UHC data are derived from all admissions under the age of 18 at a participating university hospital. The UHC data are not as detailed since it does not include the host of physiologic data that contribute to mortality prediction tools. Assuming there is accurate and complete coding of patient diagnoses (which is often not a safe assumption), comorbidities and complications included in these databases may provide sufficient information to formulate predictive models for costs and length of stay.

APR-DRGs were developed as a joint venture between the 3 M company and the Children's Hospital Association.

Case Mix Index (CMI) refers to a relative complexity and cost value assigned to a diagnosis-related group (DRG or APR-DRG).

Both data consortiums utilize the All Patients Refined Diagnosis-Related Groups (APR-DRGs) classification system. The CMS (Center for Medicare and Medicaid Services) Diagnosis-Related Group (DRG) system was developed as part of the Inpatient Prospective Payment System (IPPS) to sort patients into groups for the purpose of defining payments to hospitals for the Medicare population only. APR-DRGs were developed as a joint venture between the 3 M company and NACHRI (now CHA). Each APR-DRG has four severity levels, and there are separate adult and pediatric diagnoses. Thus, the APR-DRG system adds a great deal more specificity to the analysis of pediatric inpatient care.

Case Mix Index (CMI) refers to a relative complexity and cost value assigned to a diagnosis-related group (DRG or APR-DRG). These were developed by analyzing average estimated costs and resource utilization by primary diagnosis. Thus, a more costly and resource-intensive diagnosis is assigned a higher CMI. This way, large patient populations can be compared in terms of average CMI. A hospital with a higher average CMI cares for a larger proportion of more complex patients. As a further refinement, the more recent versions of the APR-DRG system assign four levels of severity (minor, moderate, major, or extreme) CMI values within each APR-DRG.

Certain APR-DRG designations are associated with high PICU utilization; thus, PICU care and efficiency are the primary drivers of their associated cost and LOS.

The CHA Inpatient Essentials database for 2018 includes 80 member hospitals submitting full cost (estimated from charges), length of stay (LOS), and diagnosis coding. Reports available to data-submitting institutions include comparison to multiple peer groups of the average CMI, LOS, costs, and estimated projected mortality. Estimated mortality prediction is not as accurate as the VPS system since risk adjustment is limited to models utilizing diagnosis coding only. Data for cost and LOS are adjusted according to CMI, correcting for case complexity. Cost data is also "wage adjusted" meaning that it is adjusted for personnel costs unique to each geographic area. Data is available for multiple levels of inquiry starting with executive summary data that averages all discharges at the institution for the chosen time period. Potentially more useful reports relate data by service line (respiratory medical, cardiac surgical, etc.) or by individual APR-DRG and even by APR-DRG severity group.

The data submitted to CHA includes the entire hospital stay (i.e., ICU, intermediate care unit, and general inpatient care areas as appropriate). Certain APR-DRG designations are associated with high PICU utilization; thus, PICU care and efficiency are the primary drivers of their associated cost and LOS. For example, APR-DRG #130, Respiratory Diagnosis with

Ventilator Support >96 h, defines a patient population for whom costs are heavily driven by PICU care. In addition, there are several other high-volume and lower-acuity respiratory system APR-DRGs for which cost and LOS are determined primarily by intensive and intermediate care. Approximately 80% of institutions submitting data to VPS provide intermediate care within the PICU, so the cost and LOS data for these APR-DRGs represents PICU team care.

In examining costs and length of stay data for PICU-driven APR-DRGs, I found it useful to exclude outliers since these patients markedly skewed the data. The CHA Inpatient Essentials database includes both low and high cost and LOS outliers; the high cost and LOS outliers skew the results, obscuring the interpretation of mean LOS and cost data. Examination of the data with outliers removed provides a more reliable indicator of the efficiency of care for an institution's most common patients. Inclusion of outliers in the primary analysis prejudices the data against institutions that provide care for a greater number of patients with severe chronic underlying conditions. However, when preparing reports for institution leadership, I commonly report outlier percentages in addition to the quantitative data excluding outliers. I believe that while many outliers are innate (i.e., determined by preexisting conditions), others result from therapeutic misadventures. For example, an infant status post liver transplantation admitted with RSV pneumonitis will likely be a high cost and LOS outlier in APR-DRG #130. However, so will a previously healthy infant with RSV pneumonitis who is permitted to self-extubate while vomiting and aspirating nasogastric feedings, developing aspiration pneumonitis. Thus, the ideal profile representing quality performance for PICU-driven APR-DRGs is a comparatively lower CMI and wage-adjusted cost and LOS for inlier only data, with an overall lower percentage of high outliers. One could argue that, since LOS is the major driver of cost, only adjusted costs are significant. However, in an era of periodic bed shortages, LOS needs to be an independent performance indicator since it may represent the availability of a bed for the next patient.

High cost and LOS outliers introduce skewness and some degree of unreliability to the data.

Some outliers may be predetermined and inevitable, due to preexisting conditions, while others result from deficiencies in care processes.

In addition to examining the SMR for PICU cases available through VPS, we need to evaluate the efficiency with which we manage these resources. Besides reporting the successful use of supportive interventions for respiratory failure or oliguric acute kidney injury, we also need to focus on how to improve innate respiratory or renal function, obviating the need for expensive supportive interventions. For example, high flow nasal cannula (HFNC) therapy is widely used for children requiring oxygen but is of unproven efficacy and does not improve innate pulmonary function. We previously piloted allowing HFNC and acute BiPAP in the intermediate care unit. The experiment ended when it was clear that patients were being parked on these supportive therapies for days on end with no pharmacologic therapy to enhance pulmonary function. Since then, all patients at our institution needing HFNC or acute BiPAP are placed in the PICU. Although it is reasonable to assume that this approach would increase cost and LOS, our data show that for the respiratory service line in the CHA Inpatient Essentials database, our institution is consistently in the top performing quartile for cost and LOS, regardless of the comparison group. We believe this is because we address pulmonary dysfunction using a therapeutic approach aimed at improving pulmonary function (airway resistance and lung compliance), which liberates patients from supportive devices, allowing them to more rapidly transition from the PICU to home. One of the attractions of the critical care environment is the ability to test and evaluate physiology.

The technology we employ is exciting and innovative, especially to our younger physicians, but I believe that the greatest intellectual challenge is in understanding and optimizing physiology.

VPS reports have been very useful self-examination tools for many institutions.

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50.7 Future Directions

50.7.1 Quality Measures

Where do we go from here? How do we advance beyond our initial successes by evaluating and reporting outcome measures that can be adapted into optimal care models based on evidence-based practice? The VPS SMR are very useful self-examination tools for many institutions; however, their use is not mandated for every PICU. Similar to reimbursement for transplantation services in adults, ongoing accreditation and payment for care should be outcome dependent. This requires a commitment from healthcare systems to invest in the infrastructure to support collection and analysis of outcomes that matter to patients, such as functional outcome following hospitalization.

Pediatric critical care practitioners should take the lead in advocating for the most appropriate tools to be used as quality measures in the evaluation of pediatric critical care. Hopefully, we can evolve beyond just using process measures, such as compliance with urinary catheter insertion bundles, as quality measures. In addition, tracking outcomes such as the CLABSI and CAUTI rates that currently penalize PICUs which decrease the utilization of these catheters. Instead, we need a better method to quantify an absolute reduction in these adverse patient outcomes.

There are numerous resources available to the PICU practitioner regarding quality education, performance improvement, pediatric quality measure programs, and collaborative networks. Some of these are listed in Table 50.2.

Table 50.2 Selected resources for the pediatric critical care practitioner

Learn more about	Resource	URL
QI methods for practice	AAP Quality Improvement Toolbox	► https://www.aap.org/en-us/professional-resources/quality-improvement/Pages/Quality-Improvement-Implementation-Guide.aspx
	IHI PDSA Worksheet (requires free registration to IHI site)	► http://www.ihi.org/resources/Pages/Tools/PlanDoStudyActWorksheet.aspx
	AAP education in Quality Improvement in Ped Practice	► https://www.aap.org/en-us/professional-resources/quality-improvement/Pages/default.aspx
General quality measures inventories	AHRQ National Quality Measures Clearinghouse	► https://www.ahrq.gov/gam/index.html
	Center for Medicare and Medicaid Services (CMS) Quality Measures Inventory	► https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/QualityMeasures/CMS-Measures-Inventory.html
	AMA Physician Consortium for Performance Improvement (PCPI)	► https://www.thepcpi.org/default.aspx
	Patient-Centered Outcomes Research (PCORI) – fund POEMs (patient oriented evidence that matters) research including pediatric studies	► https://www.pcori.org/
	NCQA HEDIS measures	► https://www.ncqa.org/hedis/
Pediatric quality measures program	AHRQ Pediatric Quality Measures Program (PQMP)	► https://www.ahrq.gov/pqmp/index.html

Table 50.2 (continued)

Learn more about	Resource	URL
	Children's Hospital Association (CHA) Quality Improvement	► https://www.childrenshospitals.org/Quality-and-Performance/Quality-Improvement
	Academic Pediatrics Supplement on Quality Improvement	► https://www.academicpedsjnl.net/article/S1876-2859(13)00248-9/fulltext
	Core Set of Children's Health Care Quality Measures (CCS)	► https://www.medicaid.gov/medicaid/quality-of-care/performance-measurement/child-core-set/
	Virtual PICU	► http://vpicu.net/
Quality improvement collaborative networks	AAP Quality Improvement Innovation Networks (QuIIN)	► https://www.aap.org/en-us/professional-resources/quality-improvement/Pages/Quality-Improvement-Innovation-Network.aspx
	Pediatric Research in Inpatient Settings (PRIS)	► https://www.prisnetwork.org/
	Pediatric Acute Lung Injury and Sepsis Investigators (PALISI)	► https://www.palisi.org/
	STS Congenital Heart Surgery Database (STS-CHSD)	► https://www.sts.org/registries-research-center/sts-national-database/sts-congenital-heart-surgery-database
	Pediatric Cardiac Critical Care Consortium (PC^4)	► https://pc4quality.org/
Pediatric patient safety	Solutions for Patient Safety – includes substantial resources including training videos	► https://www.solutionsforpatientsafety.org/
	AHRQ Patient Safety Network-Pediatrics	► https://psnet.ahrq.gov/search?topic=Pediatrics&f_topicIDs=335
	Paediatric International Patient Safety and Quality Community (PIPSQC)	► https://www.pipsqc.org/

50.7.2 Practice Development

As stated in the introduction, there are methods by which pediatric critical care physicians can acquire knowledge in the absence of well-designed clinical trials. Data from studies on critically ill adults can stimulate questions relevant to children. There also is a great potential for reflective learning in a specialty characterized by complex monitoring and data gathering, presenting an opportunity for physiologic correlation and reasoning. As an example, the frequent monitoring of complete blood counts along with continuous hemodynamic monitoring in children resuscitated from pediatric near drowning and other global anoxic events afforded the opportunity to observe the temporal relationship between the onset of neutropenia and the development of refractory shock and hypoxemia in many of these patients. This observation raised the question as to whether the neutropenia represented sequestration of polymorphonuclear cells in ischemic tissues during reperfusion injury or did the neutropenia represent the effect of overwhelming infection from immune barrier disruption or simply predispose to such.

The potential for reflective learning is great in a specialty where monitoring and data gathering is as involved as ours, presenting opportunity for physiologic correlation and reasoning.

To date there has been no prospective randomized controlled trial of fluid management in pediatric ARDS.

Historically, these postarrest children were not treated on admission with antibiotics since the teaching was that prophylactic antibiotic use would select for resistant organisms and the indication for antibiotics for aspiration pneumonia required the presence of fever and pulmonary infiltrates. Initial studies of antimicrobial therapy at the onset of neutropenia in these patients had limited success, but then subsequent practice evolved to administering broad-spectrum antimicrobial coverage upon admission following resuscitation from cardiac arrest, prior to the development of neutropenia. Subsequent observation found that profound neutropenia with multisystem collapse rarely occurs when patients are empirically treated on admission with broad-spectrum antibacterial coverage, including coverage for gut translocation organisms. The process by which this protocol was developed could be characterized as an example of reflective learning with the steps of association, integration, validation, and appropriation. Of note, this therapeutic approach is still unproven and requires a randomized controlled trial that would have to be multi--institutional to have sufficient numbers to determine if it is effective.

There is a dearth of data from well-executed randomized controlled trials in pediatric critical care medicine. Many important questions remain unanswered; however, that is not to say that our specialty lacks any critically evaluated clinical evidence for many of our interventions. Well-designed studies performed in the laboratories of some of the most prominent investigators in critical care physiologic research in the 1980s suggested the benefit of inotropic support and diuresis in ARDS models. Subsequently, adult observational and most recently pediatric observational studies observed improved outcome with lower fluid balance. Finally, a prospective randomized study of fluid management in adults with hypoxemic respiratory failure, with additional published insights from subgroup analysis, provided further evidence. Although there are no prospective randomized controlled trials of fluid management in pediatric ARDS, this data suggests it is reasonable for pediatric critical care providers to avoid fluid overload in children treated hypoxemic respiratory failure.

50.7.3 Standards of Care

It is time to move beyond reporting outcomes of rescue measures and evolve to reporting risk-adjusted outcomes of patients with common conditions.

It is time to move beyond reporting outcomes of rescue measures (e.g., extracorporeal support, renal replacement therapy, specialized modes of ventilation, etc.) and evolve to reporting risk-adjusted outcomes of patients with common conditions. Recent efforts to develop risk stratification tools for specific disease processes appear promising. It is far more beneficial to understand which procedures result in better risk-adjusted outcomes for children with ARDS, rather than describe the outcomes for a large series of patients treated with extracorporeal support. We need more large multicentered randomized clinical trials, like the PROSpect trial for severe pediatric ARDS (▶ https://prospect-network.org/), to improve our evidence basis for development of standards of care in pediatric critical care medicine. Ultimately, it would be even more useful to study the care of critically ill children with hypoxemic respiratory failure who do not meet entry criteria for PROSpect.

Many of the practices utilized in pediatric critical care support have not been critically studied. The challenges of designing and implementing multicenter randomized controlled trials are significant. However, that is not an excuse for not pursuing thoughtful reflection and discussion. Many aspects of care are likely to affect outcome and deserve our attention. For example, some very good work evaluated the effectiveness and need for ulcer and gastrointes-

tinal hemorrhage prophylaxis in pediatric critical illness. However, when evaluating an intervention to improve performance, it is important to identify balance measures that reflect potential harm from the intervention, such as ranitidine changing the gut flora and altering the balance between a pro- and anti-inflammatory state or causing adverse effects in the premature population.

Similarly, new clinical data has caused clinicians to reevaluate their attitude regarding oxygen supplementation in critical illness, especially following return of circulation after a cardiac arrest. Mechanically ventilated children likely receive more sedation than comparably ill adults by virtue of their immaturity and uncooperativeness, but a number of our most commonly used sedative agents cause cardiac depression and are listed in the American Heart Association scientific statement on drugs as a potential cause for exacerbating heart failure. Furthermore, cohort clinical data suggest that exposure to a number of these sedative agents has adverse effects on the developing brain.

Recent survey studies document a disappointing lack of focus on nutrition support among pediatric critical care medicine practitioners. Few pediatric intensive care programs have demonstrated interest in exploring macro-nutrition and micro-nutrition to optimize outcomes, despite the issues being extensively studied in adult critical care.

These are just some of the day to day practices in pediatric critical care medicine that vary widely among programs and could be fertile areas for sharing ideas, formulating questions and planning study approaches.

50.7.4 Sharing Best Practices

More could be done to identify best practices, defined by outcomes assessment. It was hoped that the VPS database would provide sufficient data to help define best practices. Could the VPS database be used to assess the factors associated with development of oliguric AKI necessitating renal replacement therapy for fluid overload, with the hope of shedding light on best practice? One could approach the need for CVVH to treat oliguric AKI as a preventable complication in order to examine best practices for the maintenance of renal blood flow and glomerular filtration.

With respect to rapid response team activation, Peter Pronovost wrote that we should "move away from taking credit for rescuing patients … to focus on patient flow and to provide each patient with the right care at the right time."

There are institutions that pride themselves on increasing rapid response activations as a sign of increasing care quality, even though RRT activations may represent a failure of recognition and escalation of care before the RRT event to assure patients are in the right location so that they don't need to be rescued. With respect to rapid response activations, Peter Provost wrote that we should "move away from taking credit for rescuing patients … to focus on patient flow and to provide each patient with the right care at the right time." Increasing activations of the local fire department is not a prudent quality goal (though better than not responding to fires), whereas successful fire prevention training is. Implementation of a rapid response system without evaluating preceding events in a quality improvement effort is not consistent with the initially stated focus of the National Patient Safety Goal, which directed acute care facilities to develop mechanisms to respond to changes in patient condition.

Taking the idea of best practices a bit further, some proposed that we develop a public sounding board, bulletin board, or website for our most experienced and demonstrably effective (hard outcome data) programs to publish their best practices, suggestions, and protocols. This is not to suggest that any one program has all the answers, but sharing information about practices and rationales cannot help but stimulate learning.

The VPS movement toward transparency and sharing of best practices has the potential to become a powerful tool for practice improvement and standardization.

The goal is optimization and standardization of care processes such that survival is assured early and we can focus on those adjunctive therapies (nutrition, immune modulation, neuronal integrity, etc.) that place patients on the way to optimal recovery and restoration of function.

50.7.5 What Does Good Critical Care Look Like

I teach that good critical care medicine is similar to good anesthesia; it should seem boring most the time. Meticulous attention to detail, with anticipation and prevention, can obviate much of the need for emergent resuscitation and high-end technological support. One of the axioms I was taught as a fellow was "no physician has a white cloud or black cloud, some people just complain more than others." While that may be true, I prefer the axiom, "there are no white clouds or black clouds, just decisions and consequences." Much like football, the best teams are not playing exciting "2-min offense" in the fourth quarter trying to come from behind; instead they would rather run out the clock by running the football with little drama because they already have the game won. Ideally, we will move away from focusing on rescue therapies and give increased attention to prospective trials with risk-stratified patient populations to define and standardize best approaches to critical care management of large groups of patients. This way we can be reasonably assured of survival early in the critical illness (far ahead by the fourth quarter) and can focus on those adjunctive therapies (nutrition, immune modulation, neuronal integrity, etc.) that have the greatest chance for achieving optimal recovery and restoration of function. To that end, we also should move past a focus on mortality, which is easy to measure, to focusing on other outcomes that matter to patients and their families. In view of the evolution of the patient's condition following discharge, this includes developing better methods to track patients following discharge from the PICU.

Review Questions

1. All of the following statements are true concerning mortality assessment tools in pediatric critical care medicine *except*
   - A. The standardized mortality ratio (SMR) is the ratio of the number of observed to predicted mortalities for a population of patients.
   - B. The Pediatric Index of Mortality (PIM) score is more labor intensive to collect but appears to be a more accurate predictor of mortality for pediatric intensive care units in the United States.
   - C. One criticism of mortality prediction tools that collect data over many hours after admission is that the scored physiologic derangements may be care dependent.
   - D. Within the virtual PICU system, PICU admissions are divided broadly into scheduled and unscheduled groups.
   - E. The most recent refinement of the Pediatric Risk of Mortality score, PRISM IV, collects physiologic variables for the first 4 h following admission to the PICU.

2. The most accurate statement about the Society of Thoracic Surgeons Congenital Heart Surgery Database is
   - A. The STS reported outcomes are confidential in that institutions and the public cannot see each other's data.
   - B. Within the STAT scoring system, the Fontan procedure is considered a more complex and risky procedure than the arterial switch operation.
   - C. Institutions are graded according to survival outcomes into one of five performance categories.
   - D. The STS public reporting website is available to all, revealing the grading of the survival outcomes of each institution submitting data.
   - E. During the last reporting period, roughly equal numbers of institutions were assigned to each performance rating category.

3. All the following statements are true concerning outcome measures that can be applicable to pediatric critical care medicine *except*
   A. The two primary scoring systems for estimating the risk of mortality are the Pediatric Index of Mortality (PIM) and PRISM.
   B. The All Patients Refined Diagnosis-Related Group (APR-DRG) classification system was developed as a joint venture between 3 M Company and the Children's Hospital Association.
   C. A recent large multicenter study suggested that, compared with 20 years ago, both mortality and morbidity as a result of pediatric critical illness have decreased significantly.
   D. Cost and length of stay data, available from the Children's Hospital Association or University Hospitals Consortium, include the duration and costs of the patient's entire inpatient stay.
   E. The Children's Hospital Association Inpatient Essentials database provides information regarding cost and length of stay, which is adjusted for case complexity and regional personnel costs and can be reported by individual APR-DRG or by an entire service line.

4. Which of the following issues in pediatric critical care medicine have been satisfactorily resolved through prospective, multicenter randomized clinical trials
   A. The indications for nitric oxide in pediatric acute respiratory distress syndrome
   B. Optimal fluid management in pediatric hypoxemic respiratory failure
   C. Optimal tidal volume for the management of pediatric acute respiratory distress syndrome
   D. Nutritional strategies to optimize recovery from pediatric acute brain injury
   E. None of the above

5. The most accurate statement regarding process measures related to quality and safety associated with critical illness is
   A. The large-scale implementation of a surgical safety checklist throughout a regional single payor medical system was demonstrated to reduce complications and improve mortality.
   B. Daily chlorhexidine bathing was demonstrated to reduce the incidence of catheter-associated blood stream infections (CLABSI) in a multicenter pediatric critical care unit study.
   C. Closed system in-line suction of intubated patients was shown to reduce the incidence of ventilator-associated pneumonia.
   D. The findings regarding ventilator-associated pneumonia rates from a comprehensive audit of Medicare charts were at odds with the incidence of VAP self-reported by institutions to the Centers for Disease Control.
   E. There has been no evidence that institutions manipulate data to underreport rates of adverse events for financial gain.

Answers

1. B
2. D
3. C
4. E
5. D

Suggested Reading

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Biostatistics and Evaluating Published Studies

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Contents

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Learning Objectives

- Explain how study design impacts the strength of research evidence.
- Describe general statistical principles, including p-values and confidence intervals.
- Interpret results from logistic and other regression models.
- Describe the impact of limitations on the generalizability of study conclusions.

51

51.1 Introduction

The purpose of this chapter is to provide guidance for interpreting the statistical results of published studies. This chapter gives explicit and practical guidance for assessing strength of study designs and interpreting p-values, confidence intervals, and several common statistical models such as logistic regression. Additionally, this chapter will orient the reader to important concepts for understanding the importance, generalizability, and limitations of reported studies. Randomized controlled trials (RCTs) provide the strongest level of evidence for the effectiveness of a therapy, but if care is taken to account for potential confounding, then other designs such as observational studies may also provide strong evidence. Hypothesis testing and p-values are fundamental tools for evaluating relationships between outcomes and potential predictors. Regression analysis provides a way to assess the relationship between two or more variables. Logistic regression, Cox regression, and ordinary linear regression are common types of regression modeling in clinical research. These regression models allow for the control of potentially confounding variables. Understanding how to appropriately interpret results of these models (odds ratios, hazard ratios, and effect sizes) allows the reader to understand how the predictors relate to the outcome being modeled. Correct interpretation is especially important for evaluating the potential clinical importance of variables being modeled. In addition to correctly interpreting statistical results, it is important to understand the generalizability of the reported results in order to appropriately contextualize the findings. A careful review of study limitations, including those that may not be reported, is essential for understanding generalizability.

51.2 Study Design

This section discusses the overall level of evidence one might obtain in support of the effectiveness of a therapy based on different types of study designs. Table 51.1 summarizes, in a general fashion, the types of studies that fall into each of three categories—*Strong*, *Moderate*, and *Suggestive*. These categories may be used as an initial gauge of the strength of evidence for a particular publication that is being reviewed. However, there may be limitations which affect this interpretation; these limitations are discussed in detail in Understanding Limitations.

Randomized clinical trials (RCTs) are studies in which participants are randomly allocated to one of two or more treatments. RCTs provide the strongest level of evidence for the comparative or relative effectiveness of a therapy since, when the randomization is delivered in a valid fashion, comparisons between treatment arms are statistically valid, and observed differences in outcomes between the treatment arms are usually not attributable to bias or unobserved differences in patient characteristics between the treatment arms. This property

Table 51.1 Categories of evidence used by the Agency for Healthcare Research and Quality (AHRQ) Innovations Exchange to assess the strength of the link between an innovation and the observed results

Strength of evidence	Description of research	Examples of study designs
Strong	The evidence is based on one or more evaluations using experimental designs based on random allocation of individuals or groups of individuals (e.g., medical practices or hospital units) to comparison groups. The results of the evaluation(s) show consistent direct evidence of the effectiveness of the innovation in improving the targeted healthcare outcomes and/or processes or structures in the case of healthcare policy innovations	Randomized controlled trial
Moderate	While there are no randomized, controlled experiments, the evidence includes at least one systematic evaluation of the impact of the innovation using a quasi-experimental design, which could include the non-random assignment of individuals to comparison groups, before-and-after comparisons in one group, and/or comparisons with a historical baseline or control. The results of the evaluation(s) show consistent direct or indirect evidence of the effectiveness of the innovation in improving targeted healthcare outcomes and/or processes or structures in the case of healthcare policy innovations. However, the strength of the evidence is limited by the size, quality, or generalizability of the evaluations, and thus alternative explanations cannot be ruled out	Controlled trial without randomization, Prospective cohort study, Case control study
Suggestive	While there are no systematic experimental or quasi-experimental evaluations, the evidence includes non-experimental or qualitative support for an association between the innovation and targeted healthcare outcomes or processes or structures in the case of healthcare policy innovations. This evidence may include non-comparative case studies, correlation analysis, or anecdotal reports. As with the category above, alternative explanations for the results achieved cannot be ruled out	Case series, Case reports

Strength of evidence and description of research columns, but not examples of study designs, are used with permission from AHRQ

of randomized trials is why the evidence is referred to as "direct" evidence of an effect.

The *Moderate* level of evidence in Table 51.1 refers to "quasi-experimental" designs, where a randomized trial is not carried out but an effort is made to compare nonrandomized groups, or ascertain effectiveness in a single group over time, in a valid fashion. The strongest type of nonrandomized study is a cohort study, in which two or more groups of participants are followed over time and compared with respect to an outcome. Such studies are often carried out when treatments cannot be assigned in a random fashion due to ethical or logistical realities. Ethically, for example, one cannot randomize tobacco use among consenting adult patients. Similarly, logistical and ethical concerns deny researchers the ability to randomize all patients with coronary

artery disease within a hospital system who are eligible for both bypass graft surgery and catheter-based revascularization to one of the two approaches. While a sufficiently inclusive and detailed administrative database may allow researchers to prospectively compare health resource utilization between smokers and nonsmokers, or compare outcomes, including survival between patients revascularized with surgery and those treated with catheter-based approaches, the level of evidence for such comparisons is admittedly weaker than in a randomized trial. Outside the randomization setting, there may be other systematic differences between the groups predominantly responsible for the observed association with the outcomes of interest. Smokers are typically older than nonsmokers, for example, and more severe coronary artery disease is more likely to be treated with bypass surgery than less extensive disease. Thus, when evaluating the validity of cohort study results, reviewers must determine whether appropriate adjustment was made for factors that could have confounded the observed relationship between treatment and outcome. Adjustment is discussed further in Controlling for other variables.

A case control study is also classified as *Moderate* evidence. A *case control study* compares cohorts of patients with and without an outcome (e.g., a rare cancer) that are compared for past exposure to agents or conditions for which an association with the outcome is being investigated. Although not considered to provide the strength of evidence of a RCT, in certain settings where a RCT may not be ethical or practical, case control studies may prove most valuable. For example, the landmark associations of lung carcinoma with cigarette smoking and vaginal adenocarcinoma with maternal stilbestrol use were established via case control studies. However, case control studies must be carefully evaluated for their relevance, as retrospective evaluation of exposures is susceptible to potential flaws, such as recall and ascertainment bias, that do not occur in the prospective study setting, as well as estimation bias due to suboptimal matching of cases (with the outcome) to controls (without the outcome).

The *Suggestive* level of evidence includes studies such as case reports and case series, which are anecdotal reports where results are reported without comparison to a relevant control group. Therapies that show promise are quite often initially reported to the clinical community in such settings. The level of evidence is only considered *Suggestive* since, "alternative explanations cannot be ruled out" for observed absolute or relative efficacy when the setting is not at least quasi-experimental. Small case reports, for example, may involve evaluations of patients who are ideal candidates for a particular therapy and so may also have performed relatively well on other therapies, and the level of rigor in evaluation of outcomes may not be as high as in larger, multicenter, prospective evaluations.

Randomized controlled trials (RCTs) provide the strongest level of evidence for the comparative or relative effectiveness of a therapy.

These general observations about levels of evidence should be interpreted with caution and in the context of the specific studies being considered. For example, a large, rigorously controlled, nonrandomized prospective cohort study may possibly be viewed as superior in quality to a small randomized trial with substantial missing outcome data. Potential limitations are discussed in detail in Understanding Limitations.

51.3 Interpreting Results

Clinicians should develop the skills to interpret the statistical results of a clinical research study to appropriately apply the findings to patient care. While clinicians often rely on statistician collaborators to perform the statistical analyses and to aid in the interpretation of results, a clinician collaborator has the

responsibility to develop a basic understanding of the principles of interpreting statistical results. In this section, the general principles at the core of most statistical analyses are described, and those principles are applied to some of the most common methodologies.

51.3.1 General Principles

The basic methods for drawing conclusions based on clinical studies are confidence intervals and statistical tests (i.e., hypothesis tests).

51.3.1.1 Confidence Intervals

A *confidence interval* (CI) is a range of plausible values for a parameter of interest. The percentage (e.g., 95% CI) is the level of confidence. For example, there is 95% confidence that the parameter of interest is somewhere inside the 95% CI. Restated, the 95% confidence interval can be expected to contain the true value of the parameter of interest for approximately 95 out of every 100 studies in which it is used. Confidence intervals are usually reported along with a best estimate of the parameter. An interesting example comes from the Therapeutic Hypothermia after Pediatric Cardiac Arrest Out-of-Hospital (THAPCA-OH) trial.

In the THAPCA-OH trial, 295 children remaining unconscious at 38 hospitals after an out-of-hospital cardiac arrest were randomly assigned to treatment with targeted temperature management of either 33 °C (hypothermia) or 36.8 °C (normothermia) within 6 h after the return of circulation. Among the 260 evaluable subjects who had satisfactory neurobehavioral status prior to their cardiac arrest, subjects treated with hypothermia were estimated to have a 7.3 percentage point increase (95% CI, −1.5–16.1) in the probability of a good neurobehavioral outcome at 12 months compared to subjects treated with normothermia. Thus, the best estimate is that hypothermia increases the probability of a good outcome by 7.3 percentage points. However, since the confidence interval contains zero as a plausible effect, the possibility that therapeutic hypothermia has no effect at all on neurobehavioral outcome cannot be ruled out. However, the possibility that therapeutic hypothermia improves the probability of good outcome by 16.1 percentage points or more can be ruled out with high confidence. Similarly, the possibility that therapeutic hypothermia worsens the probability of good outcome by 1.5 percentage points or more can also be excluded.

Another way of evaluating the relationship between an intervention and an outcome is through hypothesis testing.

A confidence interval (CI) is a range of plausible values. If the confidence interval contains zero as a plausible effect, the possibility that the intervention has no effect at all on the outcome of interest cannot be excluded.

51.3.1.2 Hypothesis Testing

A statistical test is an evaluation of two competing hypotheses. The *alternative hypothesis* is typically that a certain relationship exists, while the *null hypothesis* is that the relationship does not exist. For example, in the THAPCA-OH trial, the null hypothesis was that therapeutic hypothermia has no effect on neurobehavioral outcome at 12 months for children experiencing an out-of-hospital cardiac arrest. The alternative hypothesis was that therapeutic hypothermia either increases or decreases the probability of a good 12-month neurobehavioral outcome, compared to normothermia. Clinical studies are typically designed with the aim of ruling out or rejecting the null hypothesis that there is no effect or relationship, in favor of the alternative hypothesis.

The *p-value* of a statistical test is a measure of the plausibility of the null hypothesis based on the observed data. Large p-values indicate a plausible null hypothesis, whereas small p-values suggest that the observed data would be unlikely if the null hypothesis were true. The p-value can be interpreted as the chance that a treatment effect at least as large as the one actually observed would have been found by chance, *if* there were truly no treatment effect at all. For example, suppose a hypothetical trial found 12% higher survival with Drug B compared to Drug A and reported a *p*-value of 0.03. This value of 0.03 indicates that if investigators were to carry out exactly this same trial repeatedly with the same number of participants, *but survival truly was the same with both drugs*, a difference of 12% or more would be found by chance only about 3 out of 100 times. In summary, the p-value is intended to summarize in a single number the concept of "are the observed results convincing?" If a reported p-value is sufficiently small, the researcher rejects the null hypothesis as implausible and concludes that the alternative is true. The value that a p-value must be in order to be considered sufficiently small (i.e., statistically significant) may vary, but p-values less than 0.05 are generally considered sufficient evidence in favor of the alternative hypothesis. Using a threshold of $p < 0.05$ ensures that the false positive rate will be no more than 5%. In other words, if the null hypothesis is true, there is no more than a 5% chance that a study would conclude otherwise using this threshold. The threshold chosen is referred to as *alpha* (α), and the false positive rate is referred to as the *type I error rate*.

As an example, in the THAPCA-OH trial, the researchers would have concluded that therapeutic hypothermia affects the mortality rate if the p-value had been less than 0.05. However, since the reported p-value was 0.14, the researchers concluded that the null hypothesis of no effect was sufficiently plausible and reported that "in comatose children who survived out-of-hospital cardiac arrest, therapeutic hypothermia, as compared with therapeutic normothermia, did not confer a significant benefit in survival with a good functional outcome at 1 year."

Hypothesis testing is a formal evaluation of two competing hypotheses. The p-value indicates the probability that a treatment effect at least as large as the one actually observed would have been found by chance, if there were truly no treatment effect at all.

An estimate and confidence interval are often reported along with a p-value. A p-value provides a quick way to determine whether sufficient evidence of a relationship exists, and the estimate and confidence interval demonstrate how large the effect might be. The results of the THAPCA-OH trial might be reported in the following way: There was no significant difference in the probability of good neurocognitive outcome at 12 months in the hypothermia group compared to the normothermia group (estimated risk difference, 7.3%; 95% CI, −1.5–16.1%; $p = 0.14$). Assuming that the same statistical approach is used to generate the p-value and confidence interval, a 95% CI will *not* include the value corresponding to the null hypothesis (e.g., a treatment difference of 0) when the p-value is <0.05.

Common Tests

The number of different statistical tests available is innumerable. However, knowing a handful of the most commonly used tests provides an advantage when interpreting the results of many clinical studies. ◘ Table 51.2 provides salient details of some of the most frequently used tests for comparing two groups.

51.3.1.3 The Concept of Statistical Power

If a study concludes that there is not a significant effect or relationship, one must consider whether the study had the ability to discern a relationship of a clinically important magnitude. *Statistical power* is the probability that a study

Table 51.2 Frequently used tests for comparing two groups

Test name	What is being assessed?	When it may be appropriate?	What a low p-value indicates?
T-test for two independent samples	Is the *average* of a specified numeric variable the same in two different groups? For example, one might assess whether the average of each subject's daily red cell transfusion volume while receiving extracorporeal membrane oxygenation is the same in survivors vs. non-survivors	The results from one group are independent from the results of the other group[a]; *and* the sample size is large *or* the specified numeric variable does not have values that are much larger or smaller than typical values (i.e., no outliers). For very small sample sizes, the variable's distribution in each sample should be approximately normal, i.e., bell-shaped	The average is larger in one group compared to the other
Wilcoxon rank-sum test, also known as the Mann-Whitney U test	Is the *distribution* of a specified numeric variable the same in two different groups? This is similar to, but not identical to, the above t-test. For example, one might assess whether the distribution of daily red cell transfusion volume while receiving extracorporeal membrane oxygenation is the same in survivors vs. non-survivors	The results from one group are independent from the results of the other group[a] Note that this test is not excessively influenced by outliers and does not rely on large sample sizes	The specified numeric variable tends to be larger in one group compared to the other
Chi-square test	Are two specified categorical variables independent? For example, one might assess whether clinician responsiveness (yes, no) to improved oxygenation following initiation of inhaled nitric oxide for respiratory failure is independent of survival to hospital discharge (yes, no). Although this example uses binary variables, the variables may have additional categories	Two categorical variables are assessed on each subject; AND A rather technical requirement is that most combinations (e.g., ≥75%) of the two variables would occur in at least a handful of subjects (e.g., ≥5) if the variables were independent. In practice, this condition is likely to be met unless one of the variables has a category with very few subjects (as might be seen when comparing rates of rare events)	There is a relationship between the two specified categorical variables

(continued)

Table 51.2 (continued)

Test name	What is being assessed?	When it may be appropriate?	What a low p-value indicates?
Fisher's exact test	Same as the Chi-square test	Two categorical variables are assessed on each subject Note that the somewhat technical assumption needed for the chi-square test regarding combinations of the two variables is *not* required for Fisher's exact test. For this reason, it is preferred when some table values are small (e.g., <5), such as for comparing rates of rare events	Same as the Chi-square test

[a]Results from one group are considered "independent" from the results of another group if the results of the second group are not connected or dependent on the results of the first group. For example, if a clinical trial has a group of subjects who receive an active treatment while a second group of subjects receives a placebo, these two groups are independent. In contrast, if a pharmacokinetic trial comparing two formulations of a drug evaluates both drug formulations in the same cohort, then the two groups (Formulation A and Formulation B) are connected or dependent because they use the same subjects. In particular, a subject's characteristics may lead to higher concentrations of the drug when administered Formulation A *and* Formulation B

will detect a statistically significant effect, given that the true effect is of a given magnitude and considering the number of study participants. A related concept is *type II error*, which occurs when a study erroneously fails to detect a relationship, i.e., when a false null hypothesis is not rejected. The type II error rate, i.e., the probability of a type II error, is referred to as *beta* (β). Power and β are directly related (power = $1 - \beta$) so that if the power is 0.90 (90%) then β is 0.10 (10%).

Power is calculated using a variety of formulas that depend on the study design and the type of outcome being analyzed (e.g., binary or continuous). Details involving power calculations are beyond the scope of this chapter. Rather, the primary objective of this section is to introduce the reader to the concept of statistical power. For a more detailed discussion of statistical power calculations, the authors suggest *The Essential Guide to Effect Sizes: Statistical Power, Meta-Analysis, and the Interpretation of Research Results* (see Suggested readings).

The concept of statistical power is paramount for the design of clinical trials. The following general relationships between power, sample size, and treatment effect magnitude are fundamental.

- Larger studies will have more power to detect a treatment effect of any given magnitude than smaller studies.
- To detect a small treatment effect with adequate power, a larger number of subjects are required than would be required to detect a larger treatment effect.

The concept of statistical power may also be useful for the interpretation of a published trial. It is expected that, during the design phase, a clinical trial should pre-specify the assumed treatment effect and other necessary technical assumptions about the outcomes; for example, when comparing continuous outcomes between two arms, estimated standard deviations are required for each study arm as well as expected mean outcomes. The significance level, i.e., false positive rate, is also pre-specified, usually but not always at 0.05. The number of participants enrolled in the trial should then be sufficiently high to detect a significant difference with substantial power, typically 80% or greater. Any quality published clinical trial should describe the concepts of assumed treatment effect, power, and significance criterion.

When a published trial is negative, e.g., $p > 0.05$, some care is required in the interpretation. One must not be too quick to declare that the studied treatment is not effective. Instead, the reader should first examine the magnitude of treatment effect that the trial was powered to detect. If the trial was only powered to detect a change in survival from 40% to 50% or more, then the reader should not necessarily rule out the possibility that the treatment improves survival from, say, 40–45%. Refer back to Hypothesis testing to review how confidence intervals demonstrate what magnitude of treatment effect is plausible and, conversely, what can be ruled out.

For non-randomized studies, the number of participants may not be modifiable, as the researcher may be working with an existing cohort or database with a fixed number of patients. However, even in this case, negative study findings should address whether the study had the statistical power to detect effects of important magnitude. In these cases, confidence intervals alone are typically utilized to determine what magnitude of treatment effect can be ruled out (see Hypothesis testing).

Statistical power is the probability that a study will detect a statistically significant effect.

51.3.1.4 Clinical Versus Statistical Significance

When the number of research subjects is very large, effects of a small magnitude may be identified as statistically significant. For example, the GUSTO trial enrolled over 41,000 patients suffering a myocardial infarction, comparing a then new and expensive thrombolytic therapy (tissue plasminogen activator (t-PA)) to the commonly used therapy (streptokinase). Rates of death or serious stroke were 6.9% with t-PA versus 7.8% with streptokinase; the difference of less than 1% was highly statistically significant. While many clinicians believe that this is a clinically important finding, as lives are being saved with the new therapy, concerns were raised about the practical importance of this small difference given the added cost of the therapy, roughly $2000 per patient.

The GUSTO trial was designed with an extremely large sample size precisely because a very small absolute benefit on reducing rates of death and stroke was believed to be critically important by the participating investigators. Nevertheless, the GUSTO example is presented here to point out that there may be instances where a treatment effect or association is reported as statistically significant, but the magnitude of the effect may not be uniformly interpretable as being of clinical or practical importance. A very large study showing, for example, a correlation between two factors that is modest in magnitude, but statistically significant, should be reviewed critically.

Both clinical and statistical significance should be considered when evaluating the potential impact of study findings.

51.3.1.5 Number Needed to Treat

Another way of gauging the potential clinical significance of reported results is the number needed to treat. If an intervention is found to improve outcomes (e.g., p-value < 0.05), the clinical significance of the finding may be conveyed as the *number needed to treat* (NNT). The NNT is the average number of sub-

jects that need to be treated in order to prevent a single poor or undesired outcome. To derive this measure, we first calculate the absolute benefit of the better treatment, i.e., the absolute decrease in rates of the poor outcome in those receiving the better treatment, compared to the inferior treatment. The NNT is then simply (1/absolute benefit).

Revisiting the GUSTO example above, the number of subjects needed to be treated with t-PA, compared to streptokinase, to prevent one additional death or serious stroke can be estimated to be

$$\left(1/\left(7.8\% - 6.9\%\right)\right) = \left(1/0.9\%\right) = 1/0.009 \approx 111.$$

Assuming that the extra cost of treatment with t-Pa at the time of the trial was $2000, this NNT implies that the "cost per patient saved from dying or having a serious stroke" was over $200,000 (i.e., 111 patients × $2000 per patient = $222,000); this quantification led to controversy about the interpretation of GUSTO, as discussed above.

The number needed to treat (NNT) is the average number of subjects that need to be treated in order to prevent a single poor outcome. Numerically, it is the reciprocal of the absolute decrease in the rate of the poor outcome in those receiving the better treatment compared to those receiving the inferior treatment.

When significant harm results from a treatment, a similar calculation can be made to determine the number needed to harm (NNH), which represents the number of subjects that need to be treated with the agent to result in one additional patient who is harmed. In addition to an estimate of NNT or NNH, the associated confidence interval can be valuable by showing the range of plausible values for NNT or NNH.

51.3.2 Interpretation of Statistical Models

Regression analysis is a methodology for assessing relationships between two or more variables.

Now that some general principles have been introduced, a description of how to interpret the results of common regression analyses can be provided. Regression analysis is a general methodology in which the relationships between two or more variables can be estimated. One variable will be considered the outcome (i.e., the dependent variable), while other variables will be considered as predictors of that outcome (i.e., independent variables).

51.3.2.1 Logistic Regression

Logistic regression is a model in which the odds of a certain outcome are associated with one or more variables. For a typical logistic regression, the outcome must have exactly two possible values (e.g., mortality vs. survival to hospital discharge). The results from a logistic regression model are expressed in terms of estimated odds ratios, confidence intervals, and p-values. The following example illustrates these concepts.

In a multicenter study of 484 pediatric subjects receiving extracorporeal membrane oxygenation (ECMO), Cashen reported the association between prematurity and mortality with an odds ratio (and 95% CI) of 2.97 (1.42, 6.21) along with a p-value of 0.004. The p-value suggests that the null hypothesis of no relationship is not plausible (since $p < 0.05$), and it is concluded that there is a relationship between prematurity and mortality. The estimated odds ratio describes the magnitude or size of this relationship. The odds ratio is defined as the estimated odds of mortality for preterm neonates divided by the estimated odds of mortality for other children studied. The reported odds ratio of 2.97 with a lower limit of the 95% CI larger than 1 suggests that the odds of mortality are greater for preterm neonates. It can be further deduced from the odds ratio of 2.97 that the odds of mortality are estimated to be 2.97 times higher for preterm neonates or, in other

words, the odds of mortality are 197% higher for preterm neonates compared to other children studied.

In the example above, the predictor, preterm neonate, was binary. However, this need not be the case. A categorical predictor may have three or more levels, or the predictor can be continuous. These configurations are important to consider, but they are not specific to logistic regression, so they are discussed separately in Categorical predictors with more than two levels and Continuous predictor variables, respectively.

Logistic regression models are commonly used to assess the relationship of one or more variables with a binary outcome.

A Careful Look at Odds Ratios

In order to prevent accidental misinterpretation from logistic regression, it is essential to understand how odds are defined. The odds of mortality are defined as the probability of mortality divided by the probability of survival. Thus, if the probability of mortality is 50%, then the odds are 0.5/0.5 = 1. If the probability of mortality is 10%, then the odds of mortality are 0.1/0.9 = 1/9. In a study of children receiving ECMO, the probability of mortality was 48% with venoarterial support versus 30% with a venovenous mode. Thus, the odds of mortality were 0.48/0.52 = 0.92 with venoarterial mode and 0.30/0.70 = 0.43 for venovenous mode. The odds ratio is then estimated to be 0.92/0.43 = 2.14. We interpret this to mean that the *odds* of mortality are estimated to be 2.14 times higher with venoarterial mode compared to venovenous mode. It is tempting to erroneously report that mortality is 2.14 times *more likely* with venoarterial mode. However, when the relative risk is calculated, i.e., the ratio of probabilities, we see that mortality is only 0.48/0.30 = 1.60 times more likely with the venoarterial mode. Odds ratios are *not* relative risks, and care should be taken to correctly interpret them. In general, the odds and the relative risk tend to be similar when the probabilities of the event are close to 0 or 1. In the example above, the probabilities were 0.48 and 0.30, which is why the odds ratio and relative risk were so different. When the event being modeled is rare, odds ratios and relative risks are so similar that one can reasonably interpret an odds ratio as a relative risk.

Receiver Operating Characteristic (ROC) Curves

One tool to assess how well a logistic regression model is able to predict its outcome is a receiver operating characteristic (ROC) curve. Since a logistic regression model fits a probability of having an outcome for each subject in the study, this probability can be used to classify a subject as having the outcome ("positive") or not ("negative"), using any chosen cutpoint. For example, in a hypothetical study of mortality, we could call all subjects with a predicted probability of death of at least 10% positives and others negatives. It is quite possible that this model could misclassify some subjects, for example, some subjects with a model-predicted probability of over 10% could have survived. The combinations of model-predicted classifications with actual classification are provided in ◘ Table 51.3.

An ROC curve illustrates the true positive rate (sensitivity) compared with the false positive rate (100% specificity), as this cutpoint for classification varies from 0% to 100%. Since the variable predicted is binary, one level is arbitrarily considered "positive." For example, if the outcome variable is mortality, one might refer to mortality as positive and survival as negative. The true positive rate is the proportion of "positives" that are correctly identified, e.g., the proportion of subjects who died for whom the model was able to correctly predict an outcome of mortality. The false positive rate is the proportion of

Table 51.3 Combinations predicted versus actual classifications

	Predicted: positive	Predicted: negative
Actual: positive	True positives	False negatives
Actual: negative	False positives	True negatives

Table 51.4 Terminology and formulas for measures of prediction accuracy

Terminology	Description	Formula
Sensitivity (true positive rate)	Proportion of actual positives that are correctly classified	True positives/(true positives + false negatives)
Specificity (1 – false positive rate)	Proportion of actual negatives that are classified correctly	True negatives/(true negatives + false positives)
False positive rate (1 – specificity)	Proportion of actual negatives that are classified incorrectly	False positives/(true negatives + false positives)
Positive predictive value	Proportion of predicted positives that are classified correctly	True positives/(true positives + false positives)
Negative predictive value	Proportion of predicted negatives that are classified correctly	True negatives/(true negatives + false negatives)

"negatives" that are erroneously classified as "positives," e.g., the proportion of subjects that survived that the model erroneously predicted would die. Formulas for true positive rate, false positive rate, and other common measures of prediction accuracy are provided in Table 51.4.

An ideal situation is to have a model that has a high true positive rate while maintaining a low false positive rate. If the receiver operating characteristic (ROC) curve (Fig. 51.1) gets close to the upper left corner (true positive rate of 100% and false positive rate of 0%), then the model is able to very accurately predict the outcome. One way of quantifying this is to report the area under the ROC curve (c-statistic). A c-statistic can range from 50% to 100%, with higher values indicating a better predictive model. An example of a ROC curve with poor ability to predict mortality in a study of ECMO is found in Fig. 51.1. Figure 51.2 illustrates an ROC curve from a model with moderate predictive ability. Both ROC curves are based on models of mortality in the same cohort. The model used for Fig. 51.2 used additional predictor variables that allowed more precise predictions.

Figure 51.1 demonstrates the ROC curve from a logistic regression model predicting mortality based only on the mode (venoarterial versus venovenous) of extracorporeal membrane oxygenation in pediatric subjects. The area under the curve is only 55% indicating a poor ability to predict mortality. (This curve is very close to a straight line, which has an area under the curve of 50%, and indicates the model has no predictive ability, since no matter what probability cutpoint is used, subjects with the outcome are not classified any more accurately than those without!)

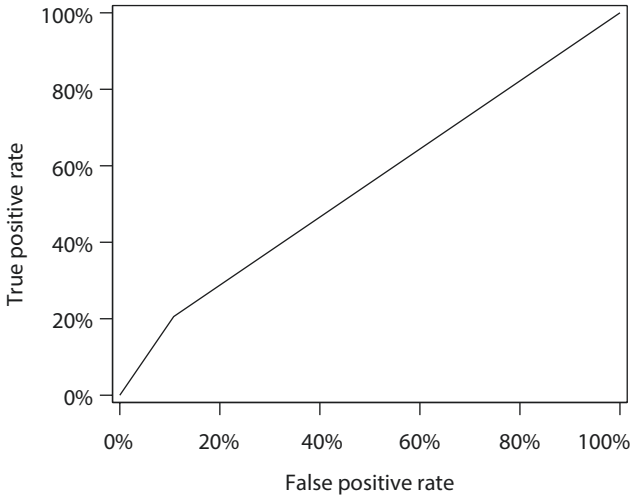


Fig. 51.1 Receiver operating characteristic (ROC) curve with a c-statistic of 55%

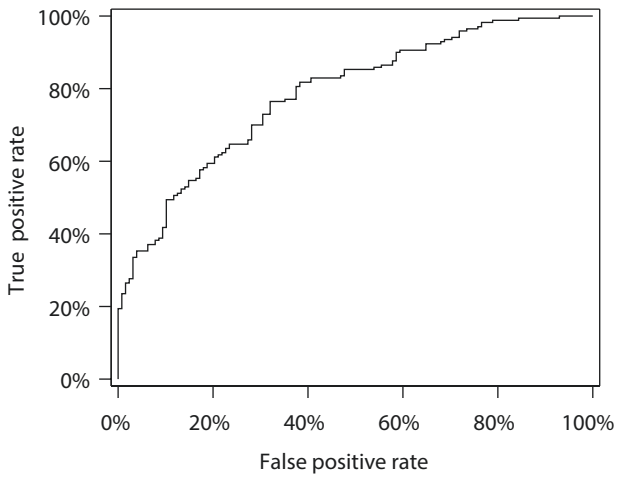


Fig. 51.2 Receiver operating characteristic (ROC) curve with a c-statistic of 79%

Figure 51.2 illustrates the ROC curve from a logistic regression model predicting mortality of pediatric subjects supported with extracorporeal membrane oxygenation. The model uses several variables including mode (venoarterial versus venovenous), age category, diagnosis of meconium aspiration syndrome, diagnosis of congenital diaphragmatic hernia, documented blood infection, indication for ECMO (eCPR, cardiac, respiratory), and the last measurement of arterial pH, partial thromboplastin time, and international normalized ratio prior to initiating extracorporeal membrane oxygenation. The area under the curve is 79% indicating a moderate ability to predict mortality.

51.3.2.2 Ordinary Linear Regression

Ordinary linear regression is a model in which the outcome, which is a continuous variable, is related to one or more variables. The latter variables may be categorical or continuous. Continuous predictor variables are discussed in Continuous predictor variables. The results from an ordinary linear regression model are expressed in terms of estimated effect sizes, confidence intervals, and p-values as illustrated in the following example.

Ordinary linear regression models are commonly used to assess the relationship of one or more variables with a continuous outcome.

In a multicenter study of 216 children receiving ECMO, researchers reported that the use of continuous renal replacement therapy was associated with a mean increase of 16.3 mg/dL (95% CI: 3.2, 29.4) in the daily plasma-free

hemoglobin concentration (p = 0.01). The low p-value suggests that the null hypothesis of no relationship between the use of renal replacement therapy and daily plasma-free hemoglobin concentration is not plausible, and it is concluded that renal replacement therapy is associated with daily plasma-free hemoglobin concentrations. The estimated effect can be interpreted as follows: subjects with continuous renal replacement therapy had, on average, daily plasma-free hemoglobin levels that were 16.3 mg/dL higher than subjects without continuous renal replacement therapy.

51.3.2.3 Cox Proportional Hazards Regression

When duration of follow-up varies between subjects, Cox proportional hazards regression can be used to assess the relationship of one or more variables with the occurrence of an event for which a cohort is at risk. Duration of follow-up and timing of events are incorporated into the analysis. This type of analysis is often referred to as survival analysis or time-to-event analysis. As with other types of regression, variables associated with the outcome may be categorical or continuous (see Continuous predictor variables). The results from a Cox regression model are expressed in terms of hazard ratios, confidence intervals, and p-values. The following example illustrates these concepts.

When duration of follow-up varies between subjects, Cox proportional hazards regression is commonly used to assess the relationship of one or more variables with the occurrence of an event for which a cohort is at risk.

In a multicenter study of 118 infants treated with endoscopic third ventriculostomy and choroid plexus cauterization (ETV + CPC) for hydrocephalus, Kulkarni identified variables associated with the risk of ETV+CPC failure, i.e., failure of the ETV+CPC to divert and reduce cerebral spinal fluid effectively. Subjects were considered at risk of failure from the date of the ETV+CPC until failure (re-operation for the treatment of hydrocephalus) or until loss to follow-up (the end of the study follow-up period, or when a specific subject could no longer be contacted). Follow-up was conducted during the study enrollment period and for 6 months thereafter. Therefore, duration of follow-up was generally longer for the first subjects enrolled than for the last. Follow-up durations varied between subjects due to the timing of enrollment and also due to subject-specific factors that precluded continued follow-up. Cox regression can, under certain conditions, appropriately handle variation in follow-up durations by excluding subjects from the "at risk" cohort after the last time of contact. From this study, researchers reported that the risk of ETV+CPC failure had a hazard ratio (and 95% CI) of 0.33 (0.10, 1.10) associated with the presence of an intraoperative clear view of the basilar artery, with a p-value of 0.07. The p-value suggests that there may be a relationship between whether the surgeon has a clear view of the basilar artery and the hazard of ETV+CPC failure. The estimated hazard ratio may be interpreted as follows: the hazard of ETV+CPC failure when there is a clear view of the basilar artery is estimated to be 0.33 times the hazard of failure when there is not a clear view. In other words, the researchers estimated that the hazard of ETV+CPC failure was 67% lower when there was a clear view of the basilar artery. However, the 95% CI indicates that the hazard of ETV+CPC failure may reasonably be as much as 90% lower or 10% higher with a clear view of the basilar artery versus without a clear view, consistent with the non-significant p-value.

51.3.2.4 Additional Concepts in Statistical Modeling

Now that some of the most common statistical modeling techniques in clinical research have been described and the manner in which they can be used to interpret study results delineated, issues that are common to all of the models previously discussed can be reviewed.

Categorical Predictors with More than Two Levels

In the previous sections, the examples were restricted to situations in which the predictor variable had only two possible values. Each of the modeling techniques previously discussed also allows predictor variables with more than two

Table 51.5 Ordinary linear regression model of daily plasma-free hemoglobin

	Plasma-free hemoglobin (mg/dL) Effect (95% CI)	p-value
Age		<0.001
Preterm neonate	−3.57 (−22.97, 15.82)	
Full-term neonate	Reference	
Infant	−2.14 (−21.26, 16.97)	
Child	−35.89 (−50.73, −21.05)	
Adolescent	−29.82 (−44.32, −15.32)	

categories. One of the categories will be chosen as the reference. Confidence intervals are presented for each category in comparison to the reference, and the width of each confidence interval is affected both by the number of subjects in the category and the number of subjects in the reference category. In the case where there are only two categories, there is often a natural reference. For example, if the variable is whether a subject received an active study drug vs. placebo, the placebo is a natural reference. If the variable is sex (male vs. female), an arbitrary choice of reference may be needed. When more than two categories exist, the choice of reference becomes more important. If there are a similar number of subjects in each category, a "natural" reference might be chosen. For example, with age categories, the youngest age category may be a natural reference. When the number of subjects in each category varies greatly, the category with the most subjects is often chosen as the reference. The category with the most subjects may be considered a natural reference, but more importantly, this approach reduces the widths of the confidence intervals that compare this category to all others.

When interpreting regression models with a categorical predictor variable, all categories are compared to a reference category.

An example from a study of children supported with ECMO reveals the results of ordinary linear regression modeling with a five-level categorical variable (Table 51.5). All age categories are compared to the reference group, in this case full-term neonates. The low p-value indicates that there is a relationship between age group and daily plasma-free hemoglobin levels. However, this does not indicate that a specific group has different plasma-free hemoglobin levels—just that there are differences between groups. The confidence intervals illustrate more clearly where the differences might be. In this example, the child age group appears to be the most different age group compared to the full-term neonate age group, and we estimate that subjects in the child age group have, on average, a daily plasma-free hemoglobin concentration that is approximately 36 mg/dL lower than subjects in the full-term neonate group.

Continuous Predictor Variables

Continuous variables are measurements that can be any number within an interval, rather than predefined numbers or categories. Examples include height, weight, and drug dose. Continuous variables can be included as predictor variables in any of the modeling approaches previously discussed. The interpretation of the results is slightly different for continuous predictor variables. Odds ratios, effect sizes, or hazards ratios for a continuous predictor variable show the magnitude of the association *for each increase of one unit* in the predictor variable.

For example, in an ordinary linear regression model of plasma-free hemoglobin concentration (mg/dL) predicted by weight (kg), if the estimated effect is −0.5, then plasma-free hemoglobin concentration decreases, on average, by

0.5 mg/dL for each 1 kg increase in subject weight. Importantly, a reader should not necessarily interpret an estimate of −0.5 to be of little clinical importance. In order to appropriately assess the importance of weight in predicting plasma-free hemoglobin, one should consider the range of typical values of weight. Thus, for a 10 kg increase in weight, we would expect a 5 mg/dL decrease in plasma-free hemoglobin concentration. If subjects in our cohort have weights that typically vary by 10 kg or more, it would be more appropriate to consider whether a 5 mg/dL difference in plasma-free hemoglobin level is clinically relevant.

The interpretation is similar, but not identical, for continuous predictor variables in logistic or Cox regression. For example, researchers found that the highest lactate concentration (mmol/L) in the first 48 h after initiation of ECMO is associated with risk of in-hospital mortality. In particular, they reported an odds ratio (and 95% CI) of 1.13 (1.09, 1.17) and a p-value of <0.001. This is interpreted to mean that for each increase by 1 mmol/L in lactate, the odds of mortality are multiplied by an estimated 1.13 or, in other words, are increased by 13%. Suppose lactate is typically around 5 mmol/L in this population and 25% of the population had a lactate 10 mmol/L or higher. In order to fully appreciate the clinical importance of this relationship between lactate levels and mortality, we can calculate how much the odds of mortality increases when lactate is increased by 5 mmol/L. The odds ratio for an increase of 5 mmol/L is $(1.13)^5 = 1.84$. Thus, the odds of mortality increase by 84% when the lactate level increases by 5 mmol/L. Hazard ratios for continuous variables in Cox regression are interpreted analogously by replacing "odds" with "hazard."

When interpreting regression models with a continuous predictor variable, the reported odds ratio, effect, or hazard ratio is for each one unit increase in the predictor variable.

Using continuous predictors in regression modeling requires caution. If a continuous predictor is included in the model (in the standard way), then increasing the value of the predictor will either (1) always increase the expected outcome or (2) always decrease the expected outcome. In particular, a regression analysis cannot appropriately capture the relationship when both low and high values of the predictor are associated with a higher outcome, while moderate values of the predictor are associated with a lower outcome. Thus, assuming the standard, linear relationships between predictors and outcomes may not be sufficient. For example, researchers demonstrated that lower values of arterial oxygen (PaO_2) in the first 48 h of ECMO were associated with lower risk of in-hospital mortality, until the PaO_2 reaches levels below 60 Torr. PaO_2 values < 60 Torr were associated with a higher risk of mortality, as were PaO_2 levels > 300 Torr. A relationship such as this is often referred to as U-shaped because when the probability of mortality is plotted against PaO_2, the curve looks somewhat like a U (Fig. 51.3). In particular, risk of mortality begins high, decreases as the PaO_2 increases, and then increases when the PaO_2 increases further. Appropriate approaches to modeling this U-shaped relationship may include (1) partitioning PaO_2 into nominal intervals to create a categorical variable (e.g., <60, 60–200, 201–400, >400 Torr), (2) excluding subjects with PaO_2 < 60 Torr, or (3) including both PaO_2 and $(PaO_2)^2$ as predictors in the model to capture the U-shape.

Controlling for Other Variables

Controlling or adjusting for variables means that those other variables are included as predictors in the regression model. This can prevent these variables from confounding the effect of other variables on the outcome.

Each type of model previously discussed can account for one or more explanatory variables. A model with a single predictor variable is referred to as a univariable model, whereas a model with two or more predictor variables is called a multivariable model. The concept of including additional predictor variables is that there are often multiple variables that are associated with the outcome, and those variables may be related to each other. For example, pump type (centrifuge versus roller head) for children receiving ECMO may be associated with the risk of mortality. Clinical site in a multicenter study may also be associated with the risk of mortality for various reasons. Consider the scenario in which

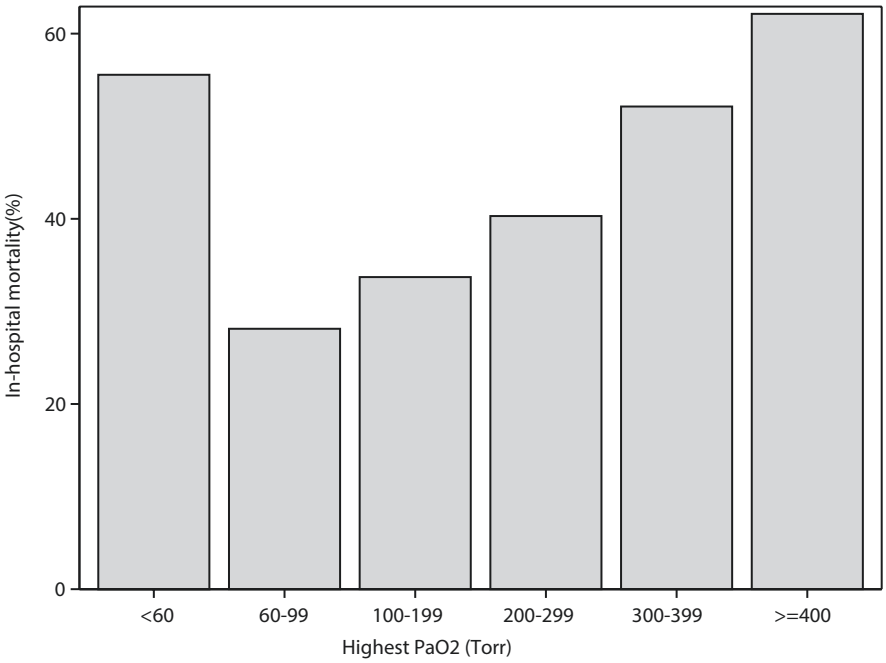


Fig. 51.3 U-shaped relationship between highest PaO_2 in the first 48 h of extracorporeal membrane oxygenation and in-hospital mortality rate. (Copied with permission from: Cashen et al. (2018))

pump type is the only predictor in a logistic regression model of in-hospital mortality. In this scenario, we might estimate that the odds of mortality are 37% lower (odds ratio 0.63; 95% CI; 0.44, 0.91) with the centrifuge pump compared to the roller head pump ($p = 0.01$). However, there are certainly additional variables that influence the risk of mortality, including the clinical site. If clinical site is included in addition to pump type in the model, it is estimated that the odds of mortality are only 31% lower with the centrifuge pump, controlling for clinical site. *Controlling or adjusting* for other variables means that those other variables are included as predictors in the regression model. The relationship between pump type and mortality can now be interpreted under the assumption that clinical site is unchanged. In other words, if two subjects are at the same clinical site, but one has a roller head pump and the other has a centrifuge pump, then the odds of mortality are estimated to be 31% (not 37%) lower for the subject with the centrifuge pump. However, if the new p-value for the relationship between pump type and mortality controlling for clinical site ($p = 0.13$) is considered, the conclusion that pump type is independently associated with mortality can no longer be made. It may be that the only link between pump type and mortality is that centrifuge pumps just happen to be more frequently used at hospitals which, for other reasons, have lower mortality rates. In this situation, clinical site is considered to be confounding the relationship between pump type and mortality.

Explanatory Variable Selection

Sometimes researchers attempt to identify explanatory variables associated with a specific clinical outcome, but they do not know in advance which variables might be important. In this case, a variable selection technique may be used as a data-driven approach to the identification of relevant variables. For example, in a study of thrombosis in children receiving ECMO, researchers considered many variables as potential predictors of daily thrombosis, including patient characteristics, support configuration, and severity of illness prior

to cannulation. A variable selection technique called stepwise selection was used to identify which of the considered variables are useful in a model predicting occurrence of thrombosis on a daily basis. In stepwise selection, variables are added or removed from the model one at a time until a final model is reached. At each step, the decision of which variable to add or remove from the model is often based on statistical significance. The model is declared final when a specified criterion is met, e.g., there are no additional variables that significantly contribute to the model. Although many variables were considered in the example provided, only three were included in the final model.

In contrast, a researcher may completely specify all variables that will be included in the model prior to examining the data. There are advantages and disadvantages to both approaches. A data-driven approach to variable selection provides some assurance that an important variable is not omitted. However, the confidence intervals and p-values are less rigorous when data-driven approaches are used. Stepwise selection assesses several models before identifying the final reported model. The pitfalls of testing multiple models, i.e., multiple comparisons, are described in detail in Pre-specified hypotheses. In contrast, when variables are completely specified in advance, an important variable may inadvertently be omitted, but the confidence intervals and p-values are more rigorous. Completely pre-specifying which variables will be included in a model is an opportunity to confirm a clinical hypothesis before becoming biased by current data trends that have yet to be vetted. In contrast, extemporaneous modeling decisions can quite furtively lead researchers to spurious conclusions. In this way, completely specifying the variables to be included in the model in advance can provide stronger evidence due to the integrity of the confidence intervals and p-values. However, when reviewing pre-specified models, readers should scrutinize the variables chosen. In particular, a reader should ask, "Is there a variable omitted that might be driving the result?" For example, a researcher may report that pump type is associated with mortality in pediatric ECMO but fail to consider the important relationship with clinical site. In particular, each clinical site may favor a particular type of pump and also have other unique characteristics that impact mortality. Thus, while pump type is associated with mortality, it may not be independently associated with mortality. A variable is considered to be *independently associated* with the outcome if it is associated with the outcome after controlling for other relevant variables. Researchers appropriately reported no evidence that pump type impacts mortality after controlling for clinical site.

Model selection techniques such as stepwise selection may provide some assurance that an important variable was not omitted, but the resulting p-values and confidence intervals are less rigorous.

A common approach to modeling is to do both when either approach may be criticized. To do so, researchers first completely specify the variables to be used for the primary analysis and then, as an exploratory analysis, use a data-driven approach to build an additional multivariable model from a larger pool of candidate variables. When exploratory analysis confirms the findings of the primary analysis, a reader may correctly view the findings with more confidence. An important caveat is that neither approach can account for variables that were not measured as part of the study. Authors should identify potentially important variables that were not collected in the limitations section, but it is also the responsibility of the reader to consider whether important variables were omitted.

51.4 Understanding Limitations

After reading conclusions made by research authors, readers should ask themselves if there are any plausible alternative explanations for the results other than the conclusion drawn by the author. Considering other plausible explanations tends to moderate the conclusions ultimately drawn by the reader. This

puts the current research in context and elucidates both what is known and what is not. This analytic questioning is so important to the understanding of reported research that a paragraph about specific limitations of the reported research is expected in the discussion section of manuscripts reporting clinical studies. The limitations section of a manuscript informs the reader what limitations the author considered. The reader should carefully review the limitations and be sure that the conclusions the author has drawn are still reasonable in spite of the limitations. Finally, the reader should consider what other limitations might exist. Some specific limitations that should be considered when reading the published results of a clinical study will now be reviewed.

51.4.1 Treatment Assignment

Randomized trials, if correctly implemented, assign treatments to participants without bias. The flow diagram in a trial should report whether all consented patients were randomized and whether all of the randomized patients received their assigned treatments. More than very occasional deviations from the assigned randomization may be a cause for concern.

In sufficiently large trials, randomization achieves approximate balance between treatment arms with respect to both observed and unobserved factors. Reports of randomized trials will typically show and compare distributions of key baseline factors between treatment arms. Substantial imbalance with respect to an important prognostic factor may be cause for concern, but this could be mitigated by explicitly incorporating the factor into the analysis. As an example, Willson conducted a RCT of calfactant versus placebo among 153 children with respiratory failure from acute lung injury and found an overall increased mortality in those receiving placebo (odds ratio 2.32; 95% CI; 1.15, 4.85, $p = 0.03$). However, analysis of the baseline characteristics of the two groups demonstrated that there were more immunocompromised patients randomized to the placebo group including those who had undergone bone marrow transplantation. Given the established higher mortality among the immunocompromised, the authors conducted an analysis controlling for immunocompromised state which revealed a statistically insignificant effect of calfactant on mortality (odds ratio 2.11; 95% CI; 0.93, 4.79, $p = 0.07$).

Additionally, imbalances between treatment groups in studies comparing therapies, but not involving randomization, often occur with respect to key factors. Distributions of such factors should be reported, and approaches to control for such factors should be clearly described.

Imbalance between treatment groups with respect to an important prognostic factor may confound a relationship, especially if treatment assignment is not randomized.

51.4.2 Uncontrolled Confounders

Except in very small studies, it is typically possible to control for known confounders to some extent in the ascertainment of a treatment effect. It is also possible that other unmeasured confounding factors may affect the magnitude of effects that are observed. In some settings, analyses can be conducted to assess the sensitivity or robustness of the result to possible uncontrolled confounding. For example, smoking clearly confounds the relationship between occupational exposure to toxins and lung cancer. Yet, the relationship between occupational exposure to potential carcinogens and lung cancer can be evaluated in a population with unknown smoking status, by appropriately comparing relative rates of chronic obstructive pulmonary disease (COPD) among patients in the same population who did, versus did not, develop lung cancer. Since COPD is associated with smoking, but not with occupational exposure

When controlling for potential confounders is not possible, analyses to evaluate the sensitivity or robustness of the results may be possible.

to carcinogens, these relative rates provide estimates of the confounding effect of smoking in the observed relationships between occupational carcinogen exposure and lung cancer. Another strategy is to estimate how strong the effect of an unmeasured confounder would have to be to eliminate an observed relationship of an exposure to an outcome. Whether such adjustment or robustness analysis is done or not, the possibility of confounding should always be considered in the review of any study comparing effects of therapies outside the randomized setting.

51.4.3 Generalizability

In order to contextualize research findings, it is important to identify the population to whom the results generalize. Eligibility criteria for the study should be carefully scrutinized, as should the source and location of the participants enrolled. Studies generated from a large administrative database may capture a more wide-ranging population than randomized clinical trials with extensive inclusion and exclusion criteria. In addition, studies requiring informed consent may lose generalizability, as subjects likely to consent may differ from those who refuse consent.

An important part of understanding published research is to consider to which population the reported results may generalize.

The first Bypass Angioplasty Revascularization Investigation (BARI) is an interesting case study of randomized trial generalizability. Among 353 patients with treated diabetes and multiple-vessel coronary artery disease randomized to revascularization with either angioplasty or bypass surgery, a strong and highly significant advantage in five-year survival was noted in those undergoing bypass surgery, leading the National Institutes of Health to issue an alert to clinicians recommending treatment with bypass surgery. However, in an additional 339 patients who met all eligibility criteria for BARI but refused randomization, instead receiving treatment selected by themselves and/or their medical caregiver, virtually no survival advantage was observed for surgical treatment. Patients not randomized tended to be more educated and reported better quality of life versus randomized patients, which may suggest better care of their diabetic condition. Moreover, within the nonrandomized patients, those with more extensive coronary disease were more likely to receive bypass surgery, which tended to provide more extensive revascularization in the setting of numerous, complex blockages. Therefore, the strong findings of this rigorous, multicenter trial did not necessarily even extend to all other patients with exactly the same condition treated at the same hospitals over the same time interval. While bypass surgery was likely the preferred approach for some types of diabetic patients with extensive heart disease, it would not confer a survival benefit for all such patients. In the current era of personalized medicine, where certain treatments may benefit only patients with particular genetic or biomarker-based profiles, generalizability should always be considered and assertions that a particular treatment is optimal for an entire broad population viewed with appropriate criticism.

51.4.4 Pre-specified Hypotheses

Relatively modern advances in data collection technology have increased both the quantity and scope of clinical research data on an unprecedented scale. While vast amounts of data now provide researchers with the ability to investigate essentially an unlimited number of clinical hypotheses, care must be taken not to inadvertently report that there is a "finding" or an association when truly there is not.

Hypothesis testing provides a discussion on p-values and their interpretation. The reader will note that a p-value is a statement about the probability of error. Recall that in a single study with no actual treatment effect, it is common to accept a 5% chance of a "false positive" $p < 0.05$. Put another way, there is a 95% chance we will *not* see a significant result when there is no treatment effect. Now, if a study looks at ten different outcomes and there is still truly no association, the chance of seeing *no* false positive findings can possibly be as low as 95% multiplied by itself 10 times, or 60%. If no steps are taken to control for the false positive rate, evaluating ten outcomes in a setting with truly no treatment effect will result in up to a 40% chance of seeing at least one false positive finding.

This multiple comparisons issue is a primary reason that clinical trials will typically have one, or a small number of, pre-specified primary hypothesis. More exploratory studies that look at more variables should be described as such and provide an idea of the scope of relationships that were examined. Many comparisons is not necessarily "bad"; for example, genomic studies may examine associations of thousands of single-nucleotide polymorphisms with an outcome, but these should incorporate principles appropriate for this setting in order to limit false findings.

If many statistical tests are performed, an approach to limit false positives is needed. The Bonferroni approach provides an easy to implement, but very conservative, method that can be employed by the reader.

Unless it has been specifically stated that hypotheses were specified before looking at the data, the reader of a report should assume that this is not the case. A report may include the results of many statistical tests, e.g., the correlation of five biomarkers with ten different outcomes, without any method to control the false positive rate. If no guidance is presented in the report, a conservative and easily implemented approach is a Bonferroni correction, where the statistical criterion that would have been used for a single statistical test of association (typically 0.05) is divided by the total number of tests that were performed (in this example, 0.05/50 = 0.001). Then, if the reader considers only those associations that have a $p < 0.001$ to be significant, the probability that one or more of them are really due to chance is no more than 5%, just like the criterion used for a single comparison. The Bonferroni correction is common when the number of tests is moderate. However, it is conservative, meaning that the probability of one or more false discoveries is *no more than* 5%. In practice, it can be much lower, making it more difficult to identify statistically significant findings. In particular, this approach would be too restrictive for the example above in which thousands of comparisons are made. For an overview of additional, less conservative, approaches, the reader can refer to the paper written by Chen *The false discovery rate: a key concept in large-scale genetic studies* listed in the Suggested reading.

51.4.5 Outcome

The clinical importance of the outcome(s) being evaluated in the report should also be considered. For example, hospital length of stay may be important, but mortality is much more so. The outcome studied may simply be a surrogate for an important longer-term outcome. The realities of study feasibility often require use of surrogate outcomes. For example, new functional morbidity that develops between baseline and hospital discharge might be used as a surrogate for longer-term quality of life. For surrogate outcomes, the reader should consider how strongly the surrogate and longer-term outcome are related, recognizing that an improvement in the surrogate may not always translate to an improvement in the clinically important, longer-term outcome.

Outcomes should be evaluated in an objective, unbiased fashion, in a way that minimizes sources of bias. As an example, in the THAPCA-OH trial, neurobehavioral status among children surviving at 1 year was performed by a telephone-based parental interview, using the Vineland Adaptive Behavior Scale, with the instrument administered from a single central location by an interviewer blinded to which treatment the child received.

51.5 Summary

In this chapter, we have discussed important statistical and study design concepts that should be considered in the review of a published study. Some study designs, such as randomized clinical trials, are usually considered to provide stronger evidence of an effect than others. Any type of published study must be critically reviewed to ensure that appropriate outcome measures have been used, that the data have been analyzed using an appropriate approach, and that the interpretation of the results is consistent with the analytic approach. Moreover, statistical significance, while highly important, must not be the only criterion used to gauge implications of a study. Statistical significance should be rigorously determined, with multiple comparisons limited or otherwise appropriately handled, and statistically significant effects should be justified as being of a clinically relevant magnitude. Negative reports should demonstrate whether there was sufficient power to rule out effects of a clinically important magnitude by presentation and discussion of confidence intervals for effect estimates.

Review Questions

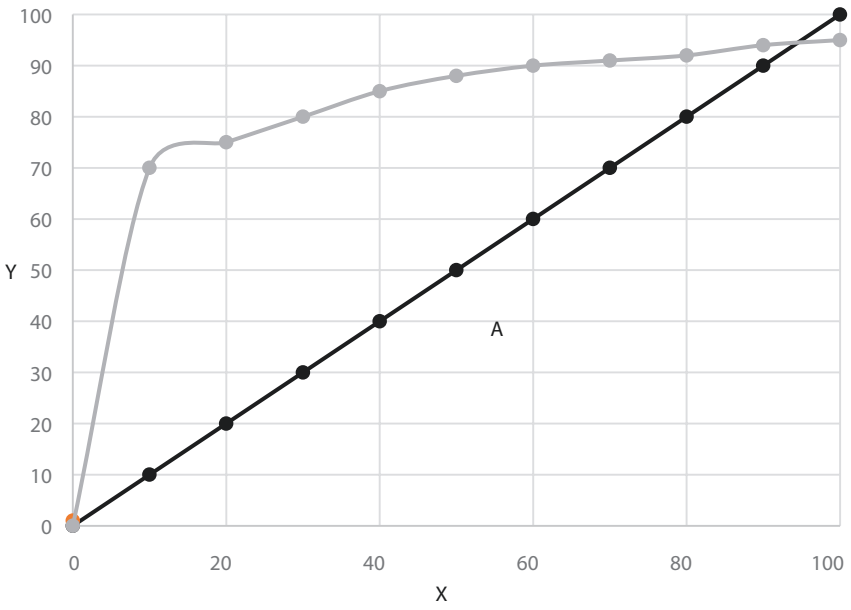
1. You are conducting a small pilot trial of a new care bundle aimed at reducing pediatric intensive care unit length of stay. It has been implemented in 15 patients to date. You are encouraged that it may be working, but it is labor-intensive. Thus, you want to analyze its effectiveness and compare the length of stay of these 15 patients with a control group in which the distributions of age, gender, and diagnosis are similar. The data are as follows.

Category	Lengths of stay (days)
Care bundle patients	2, 2, 3, 4, 4, 4, 5, 5, 7, 7, 8, 8, 10, 11, 109
Control patients	2, 4, 4, 5, 6, 7, 8, 8, 9, 10, 10, 12, 14, 17, 18

Of the following, the most appropriate statistical test to use to conduct this analysis would be:

A. Fisher's exact test
B. Paired t-test
C. Unpaired t-test
D. Wilcoxon rank-sum test

2. The following graph represents a receiver operating characteristic (ROC) curve analysis.



Which of the following best identifies the letters on the chart?

A. A = line of no prediction, X = Specificity, Y = 1 – Sensitivity
B. A = line of no prediction, X = 1 – Specificity, Y = Sensitivity
C. A = line of optimal prediction, X = 1 – Sensitivity, Y = Specificity
D. A = line of optimal prediction, X = 1 – Specificity, Y = Sensitivity

3. In the THAPCA-OH trial, among the 260 evaluable subjects who had satisfactory neurobehavioral status prior to their cardiac arrest, subjects treated with hypothermia were estimated to have a 7.3% point increase (95% CI, −1.5–16.1%) in the probability of a good neurobehavioral outcome at 12 months compared to subjects treated with normothermia. Given those findings, which of the following statements is *false*?

A. The best estimate is that hypothermia increases the probability of a good outcome by 7.3%, but that improvement is not statistically significant because the 95% confidence interval includes one.
B. The 95% confidence interval may be narrowed by enrolling more subjects, but the benefits would need to be balanced against the added costs of enrolling more patients.
C. Because the confidence interval contains zero as a plausible effect, we cannot rule out the possibility that therapeutic hypothermia has no effect at all on neurobehavioral outcome.
D. The possibility that therapeutic hypothermia improves the probability of good outcome by 16.1 percentage points or more can be ruled out with a high degree of confidence.

4. You are reviewing a manuscript that assessed the association of ten novel biomarkers with mortality among children admitted to the pediatric intensive care unit with septic shock. The authors utilized a standard p-value criterion of <0.05 to indicate statistical significance and report that three of the biomarkers are associated with mortality in this patient population citing p-values of 0.042, 0.030, and 0.025, respectively. You are concerned that the multiple comparisons increased the chance of a false positive finding by 40% (i.e., $(0.95)^{10} \sim = 0.60$ or a 40% chance of a false positive finding). Thus, you suggested that a Bonferroni correction of the p-value be made to establish a more appropriate statistical criterion to test the association of each of the biomarkers with mortality. If the Bonferroni correction approach is utilized, the p-value that should be used to establish statistical significance should be which one of the following?
   A. 0.02
   B. 0.001
   C. 0.002
   D. 0.005

5. In a hypothetical randomized, placebo controlled trial of the use of inhaled nitric oxide (iNO) among pediatric acute respiratory distress syndrome (ARDS) patients, the mortality rate was 10% among those children who received nitric oxide and 30% for those who received placebo. Which of the following values most accurately represents the odds ratio of mortality for children with ARDS treated with iNO compared to those treated with placebo?
   A. 0.11
   B. 0.26
   C. 0.33
   D. 0.43

Answers

1. D
2. B
3. A
4. D
5. B

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Supplementary Information

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